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Alveolar P_{CO_2} and P_{O_2} in pregnant and nonpregnant women at high altitude

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THE fact that the carbon dioxide tension in alveolar air during pregnancy is lower than in the nonpregnant state is well documented in the literature. That a similar phenomenon of hyperventilation occurs in patients subjected to lowered barometric

pressures at high altitude has also been well demonstrated. The latter observations have, however, always been made on nonpregnant subjects.

In the autumn of 1958, in the course of studies into the adaptive mechanisms brought into play by animals undergoing pregnancy at high altitude, we were enabled to obtain some data on the composition of alveolar air in a small group of women, pregnant and nonpregnant, residing at an altitude of 14,500 feet in Tuctu, Peru. The results obtained form the substance of this report.

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This investigation was made possible by a grant from the Josiah Macy, Jr., Foundation.

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Material and methods

All subjects in this study were living at an altitude of 14,500 feet, mean barometric pressure 456 mm. Those who were pregnant had become so at this altitude and had continued residence there during the pregnancy. Three pregnant and 4 nonpregnant women, wives of employees of the Cerro de Pasco Corporation, were available for this study. The pregnant group comprised the only known pregnant women in this small community.

All observations were made with the subjects in the resting state. All subjects had fasted and refrained from exercise, eating, or smoking for one hour prior to being studied. In the course of the next 1½ hours, with the subjects at rest under observation, three Haldane end-expiratory samples were collected in previously evacuated 25 ml. tonometers. These samples were immediately analyzed for their oxygen and carbon dioxide concentration by the method of Scholander.¹ The barometric pressure was recorded 3 hours prior to the sampling, from the only available barometer, in the Institute of Andean Biology, Morococha, Peru (altitude 14,900 feet), and the readings corrected for the 400 feet difference in altitude. The oxygen and carbon dioxide tension in the end-expiratory samples was calculated from the barometric pressure and the concentration of the gases in the samples.

The duration of pregnancy for the pregnant women was calculated from the first day of the last menstrual period. The day in the menstrual cycle on which each observation was made on a nonpregnant subject was also calculated from the first day of the last menstrual period, while the duration of the menstrual cycle was calculated from the first day of the menstrual period preceding and following the date on which the observations were made.

Results

In Tables I and II we have recorded the average for the three observations on alveolar P_{CO_2} and P_{O_2} obtained at each visit, the date of each visit being recorded. In each

case the results of the three observations lay within a range of 2 mm. for both PA_{CO_2} and PA_{O_2} . We have also recorded the duration of pregnancy in weeks for each subject in the pregnant group and the day of the menstrual cycle on which the result was obtained when the subject was not pregnant. The duration of the menstrual cycle is also given.

From these data it can be seen that for the pregnant group the mean PA_{CO_2} was 22.93 mm. Hg, with a range of 19.37 to 25.71 mm. Hg, while the mean PA_{O_2} was 59.01 mm. Hg, with a range of 54.92 to 62.78 mm. Hg.

Table I. Pregnant subjects

Gestational age	Patient	Mean P_{CO_2}	Mean P_{O_2}
37	J. U.	25.49	55.23
36	M. R.	20.03	60.88
37	J. U.	24.53	57.60
36	M. R.	20.55	59.66
37	M. R.	19.37	62.78
19	A. G.	23.55	60.53
38	M. R.	19.27	62.72
39	J. U.	22.36	59.46
40	J. U.	24.66	54.92
21	A. G.	23.01	61.05
21	A. G.	24.28	60.24
22	A. G.	25.71	56.78
22	A. G.	25.33	55.26
Mean for group		22.93 ± 0.64	59.01 ± 0.77
Range		19.27-25.71	54.92-62.78

Table II. Nonpregnant subjects

Day of menstrual cycle	Duration of cycle	Patient	Mean P_{CO_2}	Mean P_{O_2}
15	24	Th. McC.	26.72	49.14
18	30	P. S.	28.15	53.52
22	24	Th. McC.	27.00	52.76
25	30	P. S.	28.60	51.17
14	31	S. M.	30.54	49.72
9	24	Th. McC.	28.39	44.92
7	30	P. S.	27.86	47.68
24	31	S. M.	27.46	52.21
27	31	S. M.	30.37	50.94
16	24	Th. McC.	25.59	50.86
1	30	C. H.	28.55	52.60
4	30	C. H.	26.04	52.97
Mean for group			27.94 ± 0.44	50.71 ± 0.68
Range			25.59-30.54	44.92-53.52

For the nonpregnant group, the mean PA_{CO_2} was 27.94 mm. Hg, with a range of 25.59 to 30.54 mm. Hg, while the mean PA_{O_2} was 50.71 mm. Hg, with a range of 44.92 to 53.52 mm. Hg.

The data for our nonpregnant group of women compare with a mean PA_{CO_2} of 29.1 mm. Hg and a mean PA_{O_2} of 50.5 mm. Hg, obtained by Hurtado and associates² on a group of male subjects at the Institute of Andean Biology, Morococha, Peru (altitude 14,900 feet).

In Fig. 1 we have presented these data graphically by plotting the values obtained for alveolar P_{CO_2} and P_{O_2} against the day of the menstrual cycle and the week of pregnancy for the nonpregnant and pregnant subjects, respectively. Thus plotted, the data clearly demonstrate the decrease in alveolar P_{CO_2} and concomitant rise in P_{O_2} occurring during pregnancy. The changes in both PA_{CO_2} and PA_{O_2} are statistically highly significant.

Comment

The observation that the arterial or alveolar P_{CO_2} in pregnant women is significantly decreased compared with that in nonpregnant women has been noted in the literature.

Hasselbalch and Gammeltoft³ directly measured the alveolar P_{CO_2} in Haldane end-expiratory samples in 1915 and found a mean decrease in alveolar P_{CO_2} of 7.5 mm. in pregnancy in 12 cases. A lowering of 8 mm. had previously been reported in one case by Hasselbalch alone.⁴ Hasselbalch and Gammeltoft saw this decrease in alveolar P_{CO_2} as a compensatory mechanism for an "acidosis of pregnancy" and found that the pH of pregnant women at a P_{CO_2} of 31.3 mm. Hg was identical with that of nonpregnant women at a P_{CO_2} of 39.5 mm. Hg. It is interesting that they also noted two distinct decreases in alveolar P_{CO_2} of 4 to 5 mm. in the postovulatory stage of a nonpregnant women's menstrual cycle.

Aside from the above-mentioned articles numerous observations have shown that the alkali reserve of pregnant women is lower than that of nonpregnant women,^{5-13, 14}

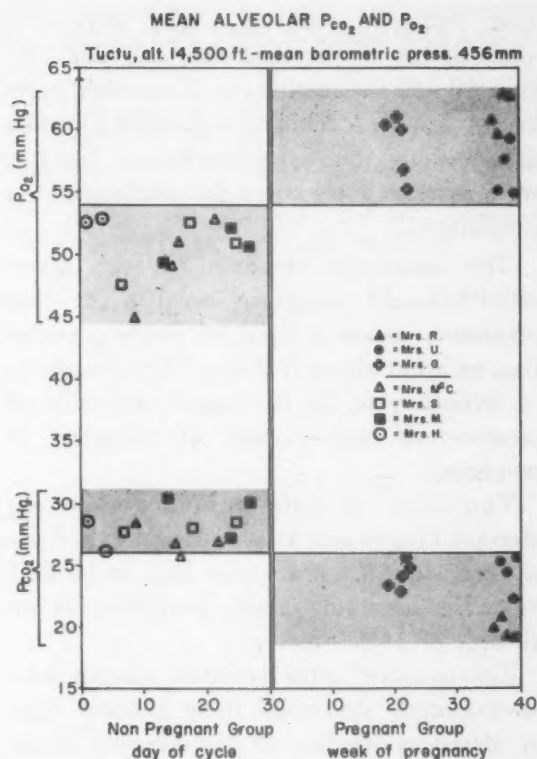


Fig. 1.

whereas the pH of blood of pregnant women did not change from that in the nonpregnant state,^{10-13, 14} so that a decrease in the PA_{CO_2} of blood can be inferred.

Döring and Loeschke,¹³ finding a decreased alveolar P_{CO_2} in the luteal phase of the menstrual cycle as well as in pregnancy, raised the question of whether this hyperventilation might be an effect of progesterone. Heerhaber, Loeschke, and Westphal¹⁵ attempted to prove that this was indeed the case by means of progesterone administration to 5 men and one postmenopausal woman, and found decreases in alveolar P_{CO_2} after progesterone administration. Similar results were thereafter shown by the careful study of alveolar P_{CO_2} in the course of numerous menstrual cycles of nonpregnant women.^{16-18, 19-23} Some of the latter articles added further data on the P_{CO_2} of alveolar air in pregnancy.

Döring, Loeschke, and Ochwaldt¹⁴ further showed that estrogens have a similar but lesser effect. In this same article they postulated that progesterone and, to a lesser ex-

tent, estrogen cause a slight respiratory alkalosis by hyperventilation so that the lowered alkali reserve is a compensatory mechanism for a primary respiratory alkalosis, rather than the hyperventilation being a compensatory mechanism for an "acidosis of pregnancy."

The consensus expressed in the above articles would, therefore, seem to be that pregnancy causes a decrease in the alveolar P_{CO_2} of approximately 8 mm. Hg, thought to be secondary to the increased production of progesterone, and possibly of estrogens, in pregnancy.

The effect of high altitude in lowering alveolar P_{CO_2} is well known. Hurtado and co-workers² found the alveolar P_{CO_2} to be 29.1 mm. Hg in young males examined at an altitude of 14,900 feet.

The question arose whether women who have already decreased their alveolar P_{CO_2} by virtue of residing at altitude will do so even further by virtue of being pregnant. From our data it is clear that this is indeed the case. It is further of interest to note that if an 8 mm. fall in alveolar P_{CO_2} occurs by pregnancy at sea level, and one of 11 mm. by residing at 14,900 feet in the nonpregnant state, our data on the PA_{CO_2} of pregnant women residing at this altitude show a decrease of approximately 17 mm. Hg, so that the two effects seem to be additive.

It is further of interest that although the rise in alveolar P_{O_2} , concomitant with the fall in P_{CO_2} occurring in pregnancy, may be of restricted benefit in pregnancy at sea level, the same cannot be said to be the case at these altitudes. Since the arterial blood is only about 81 per cent saturated with oxygen at this altitude,²⁴ each millimeter rise in P_{O_2} may be expected to be of more benefit at 14,500 feet than at sea level. It will also be apparent that at this altitude the added hyperventilation of pregnancy may be of significant benefit to a fetus dependent for his oxygen supply on the maintenance of an adequate oxygen pressure gradient across the placenta.

Summary

The alveolar P_{CO_2} of a group of pregnant women residing at an altitude of 14,500 feet was compared with that of a group of nonpregnant women residing at the same altitude.

Pregnancy is associated with a hyperventilatory effect over and above the hyperventilation already existent on the basis of residence at altitude.

We gratefully acknowledge the cooperation of the wives of employees of the Cerro de Pasco Corporation who served as the subjects for this study.

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Pressor response to angiotonin in pregnant and nonpregnant women

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VARIOUS investigators have stated that the pressor response to renal ischemia in pregnant animals differs considerably from that of nonpregnant animals. Goldblatt and co-workers,¹ and Harrison and his associates² observed a slight to moderate fall in blood pressure in hypertensive dogs and rats during pregnancy. Goldblatt³ stated that pregnant dogs are able to withstand a degree of renal ischemia not tolerated by nonpregnant animals. A similar belief is held by Corcoran⁴ and Wakerlin.⁵ Page⁶ observed that pregnant rats with renal ischemia did not develop hypertension until after parturition, and that nonpregnant hypertensive rats exhibited a lowering of their blood pressure when they became pregnant; in the rabbit the response to renal ischemia was inconsistent. MacKaness and Dodson^{7, 8} found that pregnant rats were totally refractory to the pressor action of renin although they responded to angiotonin in a manner similar to that of nonpregnant rats.

The cause of the beneficial effect of pregnancy on renal hypertension in animals is not well understood. Goldblatt and Harrison^{1, 2} attributed this effect to antipressor activities of the fetal kidneys. MacKaness⁹

showed that pregnant rats have a deficiency in hypertensinogen which may account for the lack of response to renin. On the basis of his finding of a progressive rise in blood level of angiotonase in human pregnancy, Page¹⁰ suggested that the beneficial effect in animals might be due to increased destruction of angiotonin by this enzyme. He further postulated that, because of the high titer of angiotonase during gestation, pregnant women should respond less to the pressor action of angiotonin than nonpregnant subjects. To verify this latter hypothesis, Page¹⁰ stated that he and Saperstein tested 4 nonpregnant gynecologic patients and 5 puerperal women with a standard dose of a crude preparation of angiotonin and found that the pressor response was shorter in the latter group than in the former. Although they did not test any pregnant subject for fear of an oxytocic effect of angiotonin, they concluded that the response to this agent in pregnancy should be even shorter.

Since pure synthetic angiotonin* has recently become available, we thought it would be of interest to re-evaluate the pressor response to this agent in a group of pregnant and nonpregnant women. If pregnant women have increased blood levels of angiotonase, their pressor response to exogenous angiotonin should then be less than that of nonpregnant subjects.

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**Angiotonin also called hypertensin and angiotensin was furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, in the form of angiotensin II.*

Methods and material

A total of 29 healthy subjects without any previous history of cardiovascular or renal diseases was studied. Of this number, 12 were tested during the last trimester of pregnancy and again 2 to 4 days post partum. Of the remaining 17 subjects, 13 were tested during different periods of gestation and their results were compared to those obtained from 4 nonpregnant women.

The tests were carried out in the hospital while the patients were lying supine. Control blood pressures (sphygmomanometer) and pulse rates were recorded every 2 minutes for a period of 10 minutes. Thereafter, 5 μ g of angiotonin dissolved in 0.5 ml. of isotonic saline solution was injected rapidly in one of the antecubital veins and blood pressure and pulse rate were recorded every 30 seconds for 5 minutes and then every 60 seconds for an additional period of 5 minutes. Subjective manifestations of drug action were recorded in every instance. In order to minimize variation in blood pressure recordings, all readings were taken by the same observer. The response to angiotonin was recorded as the average of the 2 highest readings following the injection of the drug. The length of action of the drug was taken at the point when the blood pressure had returned to preinjection levels.

Results

Subjective symptoms. The pregnant subjects exhibited no striking subjective symptoms in response to angiotonin. In no instance was there any evidence of an oxytocic action of the drug.

On the other hand, the nonpregnant subjects complained of a throbbing temporal and occipital headache, dizziness, dyspnea, chest oppression, palpitation, abdominal pain, and low backache. These symptoms coincided with the pressor phase of the angiotonin response and abated when the blood pressure returned to normal. No residual ill effects which could be attributed to the use of the drug were encountered.

Blood pressure response. In all patients,

the blood pressure began to rise 30 seconds after the injection of angiotonin, reached a maximum after 2 to 3 minutes, and rapidly fell to control values within the next 3 to 4 minutes.

a. Prepartum and postpartum response in the same subject. Figs. 1 and 2 compare the rise in the systolic and diastolic blood pressure in the 12 subjects tested pre and post partum. The rise was calculated as a per cent of the control blood pressure. Fig. 3 illustrates a typical example of a pre- and postpartum response in the same subject. It is evident from these figures that, in every instance, the postpartum response to angiotonin was significantly greater than that obtained in the prepartum period. The average prepartum systolic and diastolic rise in this group was 25 per cent and 36 per cent, respectively, while post partum the average rise was 55 per cent and 71 per cent, respectively.

b. Pregnant and nonpregnant women tested at random. Fig. 4 presents the average response of 6 subjects tested between 20 and 36 weeks of pregnancy, 7 between 37 and 40 weeks, and 4 nonpregnant gynecologic patients. It can be noted that the highest response to angiotonin was observed in the nonpregnant subjects and the smallest in the pregnant women near term. The response observed between 20 and 36 weeks of pregnancy was between the two extremes.

Duration of the pressor response. The average duration of the rise in the diastolic blood pressure after the injection of angiotonin was 3.6 minutes near term, 4.2 minutes between 20 and 36 weeks of gestation, and 4.7 in the postpartum and gynecologic subjects.

Pulse rate. The pulse rate decreased moderately in the majority of instances during the pressor phase of the angiotonin response and returned to control values with the fall of the blood pressure to normal.

Comment

Angiotonin is a pressor substance produced in the organism by the action of renin on hypertensinogen. It has recently been

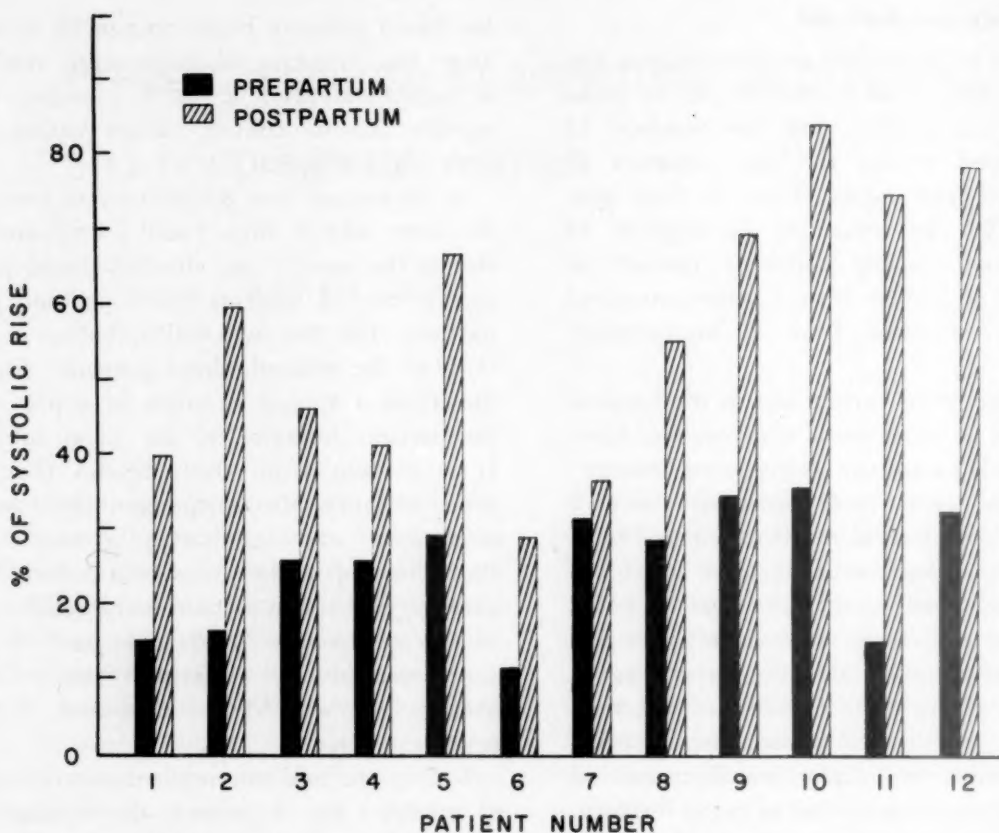


Fig. 1. Systolic blood pressure response to angiotonin of 12 subjects at term and post partum. The response was taken as a per cent of the control blood pressure. Note the striking difference between the prepartum and the postpartum response.

synthesized by Rittel and associates¹¹ and by Bumpus and co-workers.¹²

At least 2 forms of angiotonin are known to exist. The decapeptide or angiotonin I is the initial product of the action of renin on its substrate. Subsequently, this product is acted upon by an enzyme in the plasma transforming it to the octopeptide form or angiotensin II, which is a powerful vasoconstrictor substance.

It is believed that the major part if not all of the circulating angiotonin is destroyed by angiotonase.¹³ Consequently, the increase in blood level of this latter enzyme which occurs in human pregnancy, should lead to a more rapid destruction of angiotonin and, hence, to a lesser response to its pressor action. The present data confirm the above assumption since the magnitude and the duration of the pressor response to angiotonin were consistently less during preg-

nancy than after delivery. The increased pressor response in the puerperal and non-pregnant subjects, as well as the lesser response near term, as compared to an earlier period of gestation is in conformity with Page's finding of a progressive rise in angiotonase level throughout pregnancy and its rapid fall after delivery.

The present findings, however, do not agree with our recent observations in sheep and dogs in which the response to angiotonin in pregnancy was not significantly different from that of the nonpregnant state.¹⁴ Neither do they agree with those of Dodson⁸ which showed that pregnant and nonpregnant rats responded to angiotonin in a similar manner. Whether this divergency is caused by species differences cannot be stated at the present time.

It could be argued that the difference in response to angiotonin between the preg-

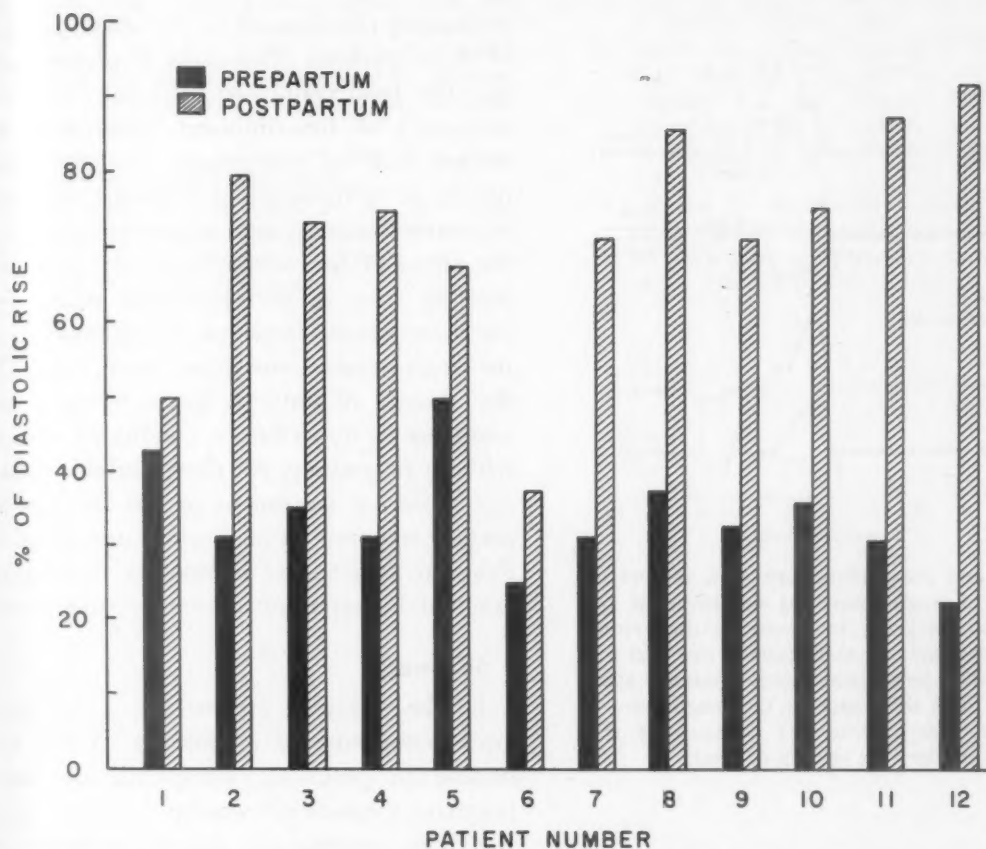


Fig. 2. Diastolic blood pressure response to angiotonin of 12 subjects at term and post partum. The response was taken as a per cent of the control blood pressure. Note the striking difference between the prepartum and the postpartum response.

nant and the nonpregnant subjects might be due to the larger blood volume which exists in pregnancy. This hypothesis, however, seems unlikely for the following reasons:

1. The pressor response to the drug was so rapid in both groups of subjects that a mixing or a dilution factor could not have played a significant role.

2. The pressor response to the drug during the seventh and eighth months of gestation, when the increase in blood volume was presumably at its peak, was higher than that at term when the blood volume had begun to fall. Had the blood volume had any influence on the response, the opposite should have occurred.

3. The pressor response in the early puerperium, when the blood volume is thought to be still somewhat elevated, was no different from that of nonpregnant sub-

jects. If the blood volume had any effect, then the response of these two groups should have been different.

All these factors seem to exclude a major role of the blood volume in the different responses to angiotonin.

It would be of interest to interpret our findings on the pressor response to angiotonin in terms of the natural behavior of renal hypertension during pregnancy. On the basis of our present observations and those of Page¹⁰ on blood levels of angiotonase, a patient with renal hypertension is expected to have a fall in blood pressure when pregnant which becomes more significant close to term. Whether this fall actually occurs cannot be stated at the present time since, in most of the reports on patients with renal hypertension followed throughout pregnancy, adequate information on the natural course of the hyperten-

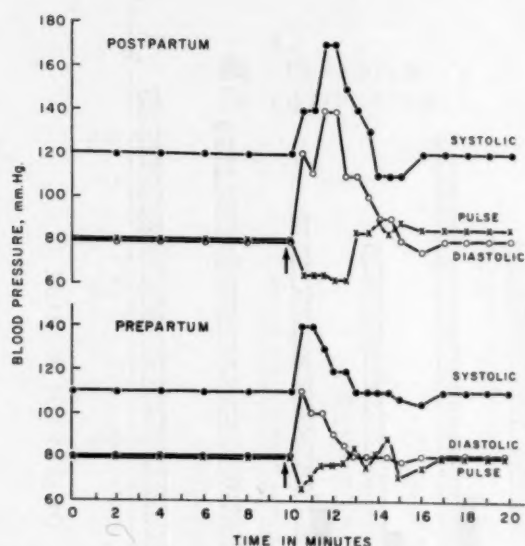


Fig. 3. Pre- and postpartum tests of a subject to whom 5 μ g of angiotonin was administered intravenously at the point indicated by the arrow. Note the marked systolic and diastolic rise and the slight fall in the pulse rate which occurred after the injection. The difference in the magnitude of blood pressure rise and in the duration of the pressor effect in the two tests is evident.

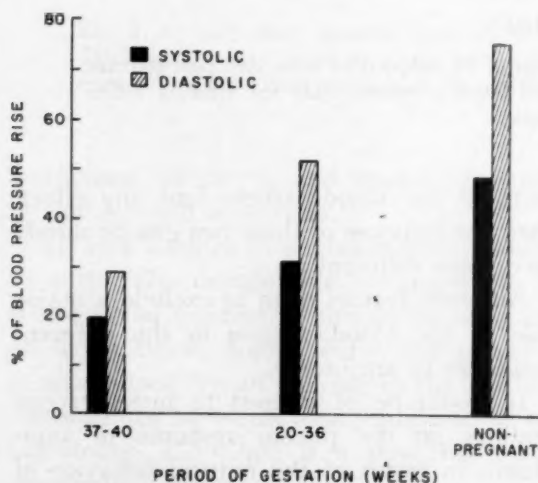


Fig. 4. Comparison of the average responses to angiotonin of subjects tested at various periods of gestation and nonpregnant gynecologic patients. Note the difference in magnitude of response in the different groups.

sion is lacking.¹⁵⁻¹⁸ The few observations made by Wilson¹⁹ have shown that the blood pressure falls in the second trimester of pregnancy but it rises to the prepregnancy level in the last trimester. Various factors contribute to the difficulties encountered in

evaluating the changes in the blood pressure of these patients. The most important are: (a) the treatment used, (b) the increased frequency of superimposed toxemia in the second half of pregnancy, (c) the complexity of differentiating between true renal hypertension and essential hypertension, (d) the effect of hemodynamic factors resulting possibly from a uteroplacental shunt, (e) the spontaneous remission or aggravation of the hypertensive condition itself, and (f) the absence of data on blood levels of angiotonase in hypertensive conditions with or without pregnancy. All these variables make any tentative assessment of our findings on pressor response to angiotonin and those of Page on angiotonase in relation to renal or essential hypertension extremely superfluous.

Summary

1. The pressor response to a standard intravenous dose of angiotonin (5 μ g) was studied in pregnant, puerperal, and non-pregnant gynecologic women.

2. The postpartum pressor response to angiotonin was significantly higher than the prepartum response when tested in the same group of patients.

3. The pressor response of the nonpregnant gynecologic patients was similar to that of the postpartum subjects. This response was greater than that observed at any period of gestation.

4. These findings were discussed in relation to the rise in plasma angiotonase level during pregnancy, and in relation to the course of renal hypertension in pregnancy.

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Protein excretion patterns in pregnancy

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PROTEINURIA is a cardinal manifestation of the toxemias of pregnancy and occurs in the absence of demonstrable disease in a small but significant number of gravid individuals. In these latter patients a 24 hour urinary protein excretion which does not exceed 0.3 Gm. is regarded as physiologic.^{1, 3} Current investigations^{5, 11, 16, 17} suggest that urinary protein composition may permit a differentiation between physiologic and pathologic proteinuria in pregnancy and may aid in distinguishing the entities which comprise the toxemias of pregnancy. The present study was undertaken for the purpose of determining the pattern of urinary protein excretion in these conditions and for evaluating this technique as a means for their differentiation.

Methods and materials

Serial, simultaneous, quantitative, and qualitative urinary and serum protein determinations were made on three to six 24 hour urine collections and corresponding daily serum samples from each of 22 hospitalized women in the last trimester of pregnancy. Total urinary protein was determined by sulfosalicylic acid precipitation.^{6, 8} Total serum protein was determined by the biuret

method.¹⁸ In these determinations, human serum protein was used as the standard and protein concentration was determined by micro-Kjeldahl nitrogen analysis employing the factor 6.25.

Electrophoretic separation of urinary and serum proteins was carried out by Durrum's method^{2, 7, 19} employing the hanging strip apparatus supplied in the Spingo Model R paper electrophoresis system. In urines with low protein content, it was necessary to concentrate the proteins by precipitation with 20 per cent trichloroacetic acid and redissolving in a diethyl barbitol buffer solution at pH 8.6. This method of concentration of the urinary proteins had no significant effect on the electrophoretic separation of the protein fractions. Protein distribution was determined by staining the paper strips with bromphenol blue and direct optical scanning by means of the Spingo Analytrol using the B-3 cam to record simultaneously the optical density and integral curves. Protein fraction concentration was expressed in terms of per cent of total protein rather than absolute amounts to avoid the error introduced by multiplying per cent values obtained in one set of units (dye-binding capacity) by total protein concentration in another set of units (biuret values).

Table I lists the clinical data pertinent to this study. The group of individuals with physiologic proteinuria in pregnancy was composed of gravidas in whom the only demonstrable abnormality was the presence of a 24 hour urinary protein excretion of

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300 mg. or less. Dieckmann's criteria³ were employed for classifying the abnormal pregnancies.

Results

Mean values and the range of total urinary and serum proteins and their fractions are summarized in Table II. Total protein values are expressed in grams. The protein fractions are expressed as per cent of dye-binding capacity.

Physiologic proteinuria in pregnancy. In this group, albumin was the predominant

Table I. Data from medical records of the 22 patients studied (all had proteinuria and were clinically grouped as indicated)

Initials	Age	Gra- vidity	Parity	Weeks of ges- tation	Remarks
<i>Physiologic proteinuria in pregnancy</i>					
J. M.	19	i	0	40	
J. J.	18	i	0	38	
E. M.	41	ii	i	36	Twins
M. H.	38	iii	ii	28	Previous eclampsia
<i>Chronic hypertensive disease</i>					
H. B.	30	ii	i	32	
T. M.	38	v	iv	40	
J. B.	32	ii	i	34	
D. E.	33	v	iii	30	Stillborn
B. H.	24	iv	iii	32	Stillborn
<i>Chronic glomerulonephritis</i>					
V. B.	18	ii	i	28	Stillborn
J. P.	29	ii	i	39	
O. W.	34	v	iv	37	
M. S.	29	ii	i	36	
E. A.	20	iv	ii	32	Stillborn
<i>Pre-eclampsia</i>					
S. R.	29	i	0	28	Stillborn
D. T.	34	i	0	34	
V. J.	28	iv	ii	39	Polyhydramnios
M. H.	26	i	0	39	Twins
L. C.	29	iv	i	36	Pulmonary arterio-venous fistula
H. A.	19	i	0	39	
<i>Eclampsia</i>					
M. T.	26	i	0	36	Twins
M. L.	29	ii	0	35	Large myomas

protein fraction. The 24 hour urinary protein excretion averaged 0.25 Gm. with a range from 0.20 to 0.30 Gm. Average values for the urinary protein constituents were as follows: albumin 64.5 per cent, alpha₁ globulin 2.0 per cent, alpha₂ globulin 5.5 per cent, beta globulin 9.9 per cent, gamma globulin 1.0 per cent. The average total serum protein was 5.50 Gm. per 100 ml. and the average values for the serum protein fractions were: albumin 49.0 per cent, alpha₁ globulin 4.2 per cent, alpha₂ globulin 12.6 per cent, beta globulin 16.5 per cent, gamma globulin 17.6 per cent.

Chronic hypertensive disease. In the individual whose pregnancy was complicated by essential hypertension, there was a relative increase in total urinary globulin as compared with the individual with so-called physiologic proteinuria of pregnancy. The average 24 hour exertion of urinary protein was 3.61 Gm. ranging from 0.77 to 12.99 Gm. The average urinary protein fractions were: albumin 61.9 per cent, alpha₁ globulin 8.9 per cent, alpha₂ globulin 7.8 per cent, beta globulin 16.3 per cent, gamma globulin 7.3 per cent. The average serum protein fractions were: albumin 37.8 per cent, alpha₁ globulin 7.6 per cent, alpha₂ globulin 16.2 per cent, beta globulin 22.5 per cent, gamma globulin 14.8 per cent.

Chronic glomerulonephritis. This group, in common with those with chronic hypertensive disease and pre-eclampsia-eclampsia, evidenced a relative increase in urinary globulin excretion. The average total 24 hour urinary protein was 3.01 Gm. with a 0.51 to 10.35 Gm. range. The average urinary protein fractions were: albumin 52.0 per cent, alpha₁ globulin 7.6 per cent, alpha₂ globulin 7.3 per cent, beta globulin 18.5 per cent, gamma globulin 14.5 per cent. The average values for the serum protein fractions were as follows: albumin 44.9 per cent, alpha₁ globulin 5.3 per cent, alpha₂ globulin 13.3 per cent, beta globulin 19.0 per cent, and gamma globulin 17.2 per cent.

Pre-eclampsia. The alpha₂ globulin fraction of the urinary protein in this group

Table II. Urinary and serum protein patterns in pregnancy (mean values and ranges)*

Type and No. of patients	Urine protein (Gm./24 hr.)	Serum protein (Gm./100 ml.)	Albumin fractions	
			Urine	Serum
Physiologic proteinuria (4)	0.25	5.50	64.5	49.0
	0.20 to	4.8 to	51.6 to	39.0 to
	0.30	6.1	77.4	57.0
Chronic hypertensive disease (5)	3.61	6.17	61.9	37.8
	0.77 to	4.2 to	56.6 to	30.9 to
	12.99	7.5	65.0	46.7
Chronic glomerulonephritis (5)	3.01	5.91	52.0	44.9
	0.51 to	4.1 to	10.2 to	23.7 to
	10.35	7.1	68.2	57.2
Pre-eclampsia (6)	1.82	5.67	52.0	36.3
	0.12 to	4.1 to	32.4 to	31.5 to
	3.77	6.6	73.7	43.3
Eclampsia (2)	6.19	5.45	36.4	42.2
	3.15 to	5.2 to	17.5 to	33.7 to
	9.23	5.6	55.4	50.7

*Albumin and globulin fractions expressed as per cent of total protein dye-binding capacity.

was approximately twice that which was obtained in the individuals with chronic hypertensive disease or chronic glomerulonephritis and the urinary gamma globulin fraction was markedly decreased relative to the serum gamma globulin. The average total 24 hour urinary protein excretion was 1.82 Gm. with a 0.12 to 3.77 Gm. range.

Table III. Albumin/globulin ratios of urinary and serum proteins in pregnancy (mean values and ranges)*

Type and No. of patients	A/G ratio	
	Urine protein	Serum protein
Physiologic proteinuria (4)	3.55	0.96
	2.67-4.56	0.64-1.32
Chronic hypertensive disease (5)	1.53	0.62
	1.31-1.87	0.46-0.87
Chronic glomerulonephritis (5)	1.08	0.82
	0.72-2.15	0.31-1.51
Pre-eclampsia (6)	1.10	0.57
	0.48-2.81	0.46-0.76
Eclampsia (2)	0.57	0.73
	0.21-1.24	0.50-1.03

*Determined from per cent of total protein dye-binding capacity.

The average values for the urinary protein components were: albumin 52.0 per cent, alpha₁ globulin 7.4 per cent, alpha₂ globulin 13.6 per cent, beta globulin 18.2 per cent, gamma globulin 8.0 per cent. Average values for the serum protein constituents were as follows: albumin 36.3 per cent, alpha₁ globulin 8.4 per cent, alpha₂ globulin 14.3 per cent, beta globulin 20.8 per cent, gamma globulin 19.8 per cent.

Eclampsia. In this group the urinary albumin, the alpha globulin and the beta globulin fractions were lower than the serum values for these components, and there was a marked relative increase in the urinary gamma globulin fraction. The average total 24 hour urinary protein was 6.19 Gm. with a 3.15 to 9.23 Gm. range. The average urinary protein fractions were: albumin 36.4 per cent, alpha₁ globulin 2.8 per cent, alpha₂ globulin 12.0 per cent, beta globulin 14.8 per cent, gamma globulin 34.4 per cent. The average serum protein fractions were: albumin 42.2 per cent, alpha₁ globulin 8.2 per cent, alpha₂ globulin 16.4 per cent, beta globulin 21.7 per cent, gamma globulin 11.5 per cent.

ions

Serum

49.0

39.0 to

57.0

37.8

30.9 to

46.7

44.9

23.7 to

57.2

36.3

31.5 to

43.3

42.2

33.7 to

50.7

Globulin fractions

Alpha ₁		Alpha ₂		Beta		Gamma	
Urine	Serum	Urine	Serum	Urine	Serum	Urine	Serum
2.0	4.2	5.5	12.6	9.9	16.5	1.0	17.6
0 to	2.5 to	0 to	8.8 to	0 to	13.9 to	0 to	11.4 to
2.6	7.3	6.6	20.8	11.9	21.3	1.4	25.0
8.9	7.6	7.8	16.2	16.3	22.5	7.3	14.8
5.4 to	5.2 to	6.5 to	11.6 to	12.8 to	18.3 to	2.3 to	10.1 to
11.1	9.8	9.8	21.3	19.5	26.1	10.4	18.9
7.6	5.3	7.3	13.3	18.5	19.0	14.5	17.2
3.4 to	3.0 to	6.1 to	7.3 to	11.0 to	7.7 to	4.1 to	10.6 to
26.2	10.6	13.5	24.1	23.8	31.0	44.0	27.0
7.4	8.4	13.6	14.3	18.2	20.8	8.0	19.8
4.8 to	5.9 to	5.3	11.6 to	0 to	19.1 to	0.8 to	16.2 to
9.0	11.3	20.0	19.0	33.1	24.0	14.0	23.5
2.8	8.2	12.0	16.4	14.8	21.7	34.4	11.5
0 to	6.4 to	10.5 to	14.1 to	12.8 to	16.0 to	18.2 to	8.2 to
4.5	9.9	13.6	18.6	16.8	27.4	50.6	14.8

Comment

The entities associated with proteinuria in pregnancy could not be distinguished by a comparison of total urinary albumin and globulin with total serum albumin and globulin, or by a comparison of the albumin/globulin ratios. Table III lists the mean values and range of the urinary and serum protein albumin/globulin ratios. Fig. 1 compares the average total albumin and total globulin values of the serum and urinary proteins. In normal pregnancy the average urinary and serum albumin/globulin ratio was 3.55 and 0.96 respectively. In chronic hypertensive disease these average ratios were 1.53 and 0.62. In chronic glomerulonephritis the ratios were 1.08 and 0.82. In pre-eclampsia, the average albumin/globulin ratios for urinary and serum protein were 1.10 and 0.57, respectively. In eclampsia the average urinary albumin/globulin ratio was 0.57 and the average serum albumin/globulin ratio was 0.73.

Fig. 2 compares the urinary and serum protein fractions. Individuals with eclampsia evidenced a marked increase in the urinary gamma globulin fraction and a lesser in-

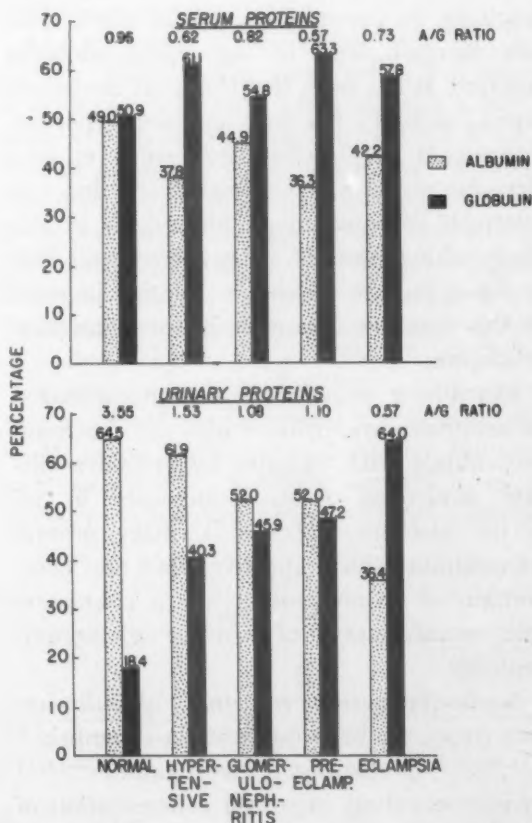


Fig. 1. Average total albumin and globulin (A/G ratio).

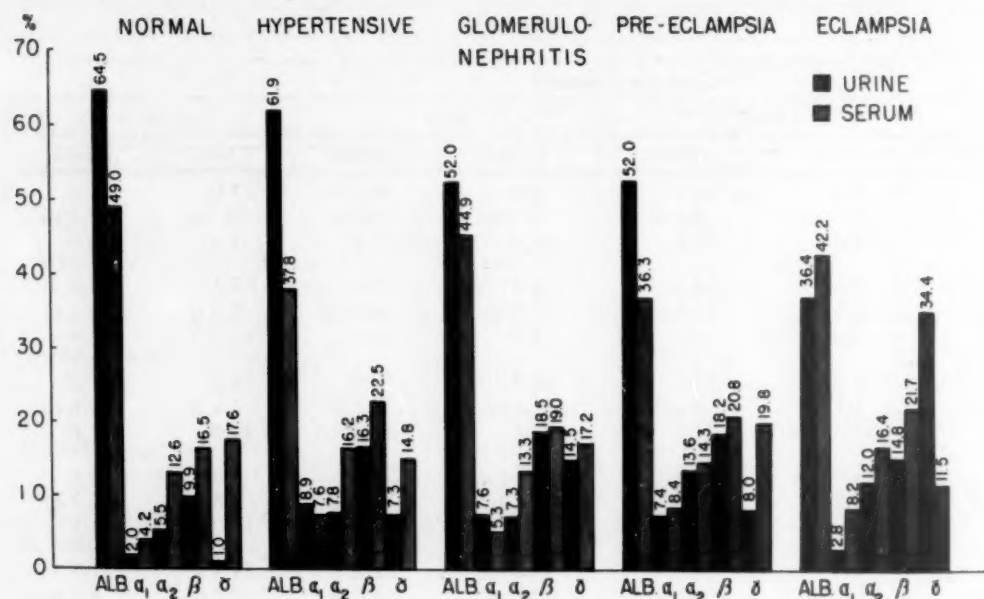


Fig. 2. Composition of urinary and serum protein in toxemias of pregnancy.

crease in the α_2 globulin fraction as compared with the corresponding serum fractions. In pre-eclampsia there was a relative increase only in the α_2 globulin fraction. It has been reported that the serum α_2 globulin fraction includes hypertensinogen. It is, therefore, interesting to note that the serum α_2 globulin fraction was relatively elevated in all individuals in this study who evidenced hypertension and that in the urine the maximum relative increase in this fraction occurred in pre-eclampsia-eclampsia.

Physiologic proteinuria was characterized by relatively low urinary globulin fractions. Individuals with chronic hypertensive disease evidenced relative increases in all of the globulin fractions. Urinary protein composition which approximated the composition of serum protein was a characteristic manifestation of chronic glomerulonephritis.

A relative increase in urinary globulin has been reported in pre-eclampsia-eclampsia.^{3, 4, 11, 15-17} Numerous investigators^{5, 9-15, 17} have reported an increased concentration of plasma α globulin in pre-eclampsia-eclampsia. Some workers^{5, 9} have reported a

relative increase in the serum beta globulin fraction in this entity while others^{10, 11} have reported a decrease in this component. Our results indicate that there is a relative increase in serum beta globulin fraction in pre-eclampsia-eclampsia.

The relative role of capillary permeability, cellular catabolism, selective filtration, tubular reabsorption, altered renal hemodynamics and extrarenal neuroendocrine factors in the etiology of the pathologic and the so-called physiologic proteinuria of pregnancy have yet to be determined. Thus the critical factors mediating the pattern of urinary protein excretion in these patients are unknown.

Summary

Serum and urinary protein fractions were determined simultaneously in a group of normal and abnormal pregnant patients by electrophoretic separation. A comparison of these urinary and serum protein fractions revealed differences in the pattern of urinary protein excretion which suggest that this method affords a means for differentiating the entities associated with proteinuria in pregnancy.

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Discussion

DR. JOHN C. BUCKINGHAM, Chicago, Illinois. We have used an entirely different method of filter paper electrophoresis to estimate serum protein fractions during pregnancy. As we have not analyzed urinary proteins, we find the present data most interesting.

Although employing the Durrum electrophoresis cell, we used bromcresyl green to stain the bands of separated protein on the filter paper strips.¹ Estimation of protein was then performed with the aid of direct densitometry. The curves plotted from these density values were subsequently corrected for dye binding of protein by Latner's method.² The areas under each segment of the resultant curves were then determined manually by planimetry and the percentage of each component calculated. All total protein and albumin/globulin ratio values were

obtained by using the biuret method on the fresh serum samples.

The summary of our present data can be seen in Table I. The mean values for serum proteins from each study group show some agreement with those of the present authors, as well as with previously reported studies.³⁻⁹ We confirm the finding of the essayists that there is an increase in the average values of serum beta and alpha globulin components in pre-eclampsia. Direct comparison of analogous data indicates definite agreement, despite independent methods of analysis. This is seen in Tables II and III.

It must be emphasized that all our values, as well as those from the present investigation, are simple means from very small samples, and that wide ranges occur in these samples. In some instances these ranges show overlapping values.

Table I. Serum protein fractions—average per cent values

Trimester and No. of patients	Gamma	Beta	Alpha ₂	Alpha ₁	Albumin	Albumin/ globulin ratio
Normal nonpregnant (7)	23.8	12.8	10.2	3.0	49.9	1.1
Normal first trimester pregnancy (6)	26.5	18.0	13.3	5.5	36.3	.58
Normal second trimester pregnancy (8)	21.5	16.5	13.3	4.9	43.7	.82
Normal third trimester pregnancy (8)	17.6	19.1	13.0	5.4	45.0	.84
Pre-eclampsia third trimester (7)	20.9	20.2	14.2	6.2	38.3	.63

Table II. Serum proteins—mean values and range normal pregnancy—third trimester

<i>Authors and No. of patients</i>	<i>Gamma</i>	<i>Beta</i>	<i>Alpha₂</i>	<i>Alpha₁</i>	<i>Albumin</i>	<i>Total protein</i>	<i>Albumin/ globulin ratio</i>
Lorincz and McCartney (4)	17.6 (11.4- 25.0)	16.5 (13.9- 21.3)	12.6 (8.8- 20.8)	4.2 (2.5- 7.3)	49.0 (39.0- 57.0)	5.50 (4.8- 6.1)	.96 (.64- 1.32)
Buckingham and Barnes (9)	17.4 (13.0- 23.4)	19.2 (14.2- 23.7)	13.0 (10.4- 17.5)	5.3 (3.4- 7.4)	45.2 (31.4- 54.5)	7.01 (6.2- 7.5)	.84 (.75- 1.2)

Table III. Serum proteins—mean values and range pre-eclampsia—third trimester

<i>Authors and No. of patients</i>	<i>Gamma</i>	<i>Beta</i>	<i>Alpha₂</i>	<i>Alpha₁</i>	<i>Albumin</i>	<i>Total protein</i>	<i>Albumin/ globulin ratio</i>
Lorincz and McCartney (6)	19.8 (16.2- 23.5)	20.8 (19.1- 24.0)	14.3 (11.6- 19.0)	8.4 (5.9- 11.3)	36.3 (31.5- 43.3)	5.67 (4.1- 6.6)	.57 (.46- .76)
Buckingham and Barnes (7)	20.9 (17.4- 26.2)	20.2 (14.2- 23.8)	14.2 (8.5- 21.2)	6.3 (2.8- 11.0)	38.4 (24.2- 53.6)	6.54 (5.6- 7.4)	.63 (.32- 1.15)

We can find no statistically significant differences between the mean values observed in our study groups, and we would ask the essayists if their data have been given statistical treatment.

In fact, it seems that all our patients may have been drawn from one statistical universe, rather than from groups differing biologically with respect to serum protein values. At present we are increasing the size of our study group samples to determine if statistical differences will then emerge.

Our experience suggests either that estimation of serum protein fractions by filter paper electrophoresis is too inaccurate to define the differences present in these pregnancy states or that no real differences exist in the individual groups studied.

It would seem, therefore, that results from protein separation by paper electrophoresis should be verified before any important interpretation concerning their biological meaning is accepted.

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DR. JOHN P. HARROD, JR., Chicago, Illinois. After the qualitative test for proteinuria became routine, its faults were recognized. It is widely known that it should be done only as a screening test and it is generally accepted that the total 24 hour quantitative test should replace qualitative studies. The addition of electrophoretic separation of the urine and serum proteins is now recommended.

Dr. Lorincz chose to use as controls 4 patients with "physiologic" proteinuria which he labeled as normal. This creates a large doubt in my opinion. Are these really "physiologic"? Has the physiologic designation diagnosis been corroborated with normal renal biopsies? The authors imply that electrophoretic studies are of value in aiding diagnosis. This value seems to be limited, however, because of the wide overlapping

of even the α_2 globulin fractions in all groups studied. Friedberg was unable to correlate the height of the alpha peak and blood pressure levels; and I would like to ask the authors if they found any such correlation. Beta globulin has been shown to increase in diseases associated with excessive atherosclerosis such as chronic hypertension. Can the authors offer an explanation for the high beta globulin levels in pre-eclampsia-eclampsia?

DR. LORINCZ (Closing). It is very difficult to make any statements concerning the questions raised because they would be purely speculative. The group here has been relatively small and the results are indicative of trends only.

In regard to the question on the correlation between α_2 globulin and blood pressure, we

found no correlation. It is interesting that in the urinary fractions the highest values were found in pre-eclampsia-eclampsia, although these patients probably had lower blood pressures as a group than did the other abnormal patients.

The elevated beta globulin levels that were questioned, occur in pre-eclampsia. Here we found that about 20 per cent of the globulin excreted was beta globulin and this was twice that found in normal pregnancy.

The serum levels were proportionally elevated in all groups except in our normal controls where the beta fraction was only 16 per cent. Any account of the elevated levels of serum beta globulin in abnormal pregnancies would be purely speculation. We also found some increase in the serum level of gamma globulin and albumin in all of the abnormal pregnancies.

Experimental hypothermia in the pregnant mouse

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IN RECENT years hypothermia has found acceptance as a valid adjunct in the management of various pathologic conditions of the central nervous system.³⁻⁶ Thus, it is only reasonable to expect that occasionally one may be called upon to administer or to decide whether to administer hypothermia to a pregnant woman.

The present scarcity of clinical material^{2, 7, 9} and the foreseeable future scarcity should not be expected to yield definitive information about the effects of hypothermia on the continuation of pregnancy. Accordingly, the present study was undertaken in the laboratory in an effort to establish whether or not the course of pregnancy is affected by hypothermia in the absence of coexisting pathologic conditions.

Material and methods

Adult female white mice in heat, as determined by simple inspection of the genitals, were exposed in groups of 3 to an adult male for a period of 72 hours. Batches of 21 female mice were mated on the same day. The rate of pregnancy which should be expected from this procedure was determined in 36 mice which were left unmo-

lest, and it was found to be 45 per cent.

The effects of hypothermia on the expected rate of pregnancy were investigated in successive batches of mice mated according to the same schedule. Hypothermia, at a rectal temperature of 26° C. for 3 hours, was induced under ether anesthesia during the first, second, or last third of presumed gestation in 26 animals. The technique employed was total body cooling by exposure to a cold atmosphere in a refrigerated pan. Immersion in ice water was not carried out at any time.

On the same day, and at the same time that the experimental group was subjected to hypothermia, a control group of mice from the same batch, that is, mated on the same day, was subjected for the same length of time to ether anesthesia only. Also, another control group from the same batch was subjected to food and water deprivation for the same length of time. Thirty-eight mice were used for the two control groups.

Results

The results are given in Table I. It may be seen that the group in which the true pregnancy rate deviated most from the expected rate was the group in which hypothermia and anesthesia were administered in the first third of pregnancy. In all other instances no significant deviations from the expected rate were found. It may be worth mentioning that deep ether anesthesia or simple food and water deprivation did not affect the pregnancy rate significantly.

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The occurrence of stillbirth was sporadic and could not be associated with any one variable or combination of variables. Both stillbirths occurring in the controls of the first third of gestation were in the same litter. Of the 5 in the group refrigerated and anesthetized during the middle third of gestation, 4 were in the same litter.

Comment

Under the conditions of the experiment the continuation of pregnancy was affected by total body hypothermia during a very specific stage of gestation. Such a statement should hardly be a novelty. It is an accepted fact that there are specific phases of gestation which are associated with peculiar pathologic or physiologic features. Thus, it is conceivable that hypothermia might exert a deleterious influence on some very special physiochemical processes related to an individual stage of embryonic or placental evolution. Smith's work⁸ with frozen hamsters fully supports this view.

What this very special stage may be for the human individual is very hard to say. The few existing reports^{2, 7, 9} deal predominantly with patients who were in the second trimester at the time hypothermia was undertaken. Also, more recent reports¹ would indicate that in the late stages of pregnancy hypothermia may even be beneficial to both the mother and the fetus. Furthermore, the diseases for which hypothermia is usually undertaken are frequently associated with hypoxia, coma, and occasionally metabolic acidosis, which may by themselves induce fetal morbidity and mortality most likely unrelated to hypothermia.¹⁰ This occurrence would tend to make the interpretation of the results difficult.

Thus, as one might have anticipated, although the available experimental material would indicate that there is a stage of pregnancy at which hypothermia will interfere with its continuation, we do not know what this stage is for humans, and conditions are such that it may be difficult to obtain this information from routine clinical observation.

In the light of these considerations preg-

Table I. Experimental results in mice

	Trimester of pregnancy		
	First	Second	Third
<i>Control</i>			
Pregnant	4	4	4
Total	9	10	9
Total offspring	33	35	26
Stillbirths	2	0	0
<i>Anesthesia (ether)</i>			
Pregnant	3	2	3
Total	7	7	6
Total offspring	22	11	23
Stillbirths	0	0	0
<i>Anesthesia (ether) and hypothermia</i>			
Pregnant	1	5	5
Total	9	9	8
Total offspring	10	24	37
Stillbirths	0	5	0

nancy should not be considered as a contraindication to hypothermia where the anticipated maternal mortality and morbidity demand immediate curative operations.

Summary

The results of controlled laboratory experiments indicate that hypothermia, if administered during the first third of gestation, may adversely affect the continuation of pregnancy in mice. These findings are discussed in their possible relation to the administration of hypothermia to a pregnant woman.

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Relaxation and psychosomatic methods of preparation for childbirth

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THE first writer to use the term "relaxation" in relation to obstetrics was the English doctor, Grantley Dick Read,²⁴ who, about 1933, developed the method of "natural childbirth." Later, the term was used in a slightly different sense by the French practitioners of the "psychoprophylactic method" (PPM) of preparation for childbirth. Again, the proponents of hypnotic methods in obstetrical analgesia use the same word, with their own particular connotation. At the moment, therefore, there is a serious confusion about the precise meaning of the term. In this study we shall attempt to clarify some aspects of this difficult problem. An examination and discussion of the ways in which relaxation is used in the different psychosomatic methods of obstetrical analgesia—Read's method, hypnotic methods, and psychoprophylactic methods—will lead us to our own formulation of a new approach to the controversial question of the nature of "relaxation" as it is used in obstetrics; and this in turn may shed some light on the idea of relaxation in general.

Read's method

Read starts from the idea that uterine contractions are physiologically painless. So-

ciocultural factors cause fear, and this fear leads to tension which, in turn, causes pain (it is a triad: fear → tension → pain). Fear is removed by education and tension overcome by relaxation. Relaxation is, therefore, an important part of the method and is practiced both during preparation and during labor. Learning to relax consists of contracting muscle groups so as to feel tension, and then decontracting them so as to experience relaxation by way of contrast. The theoretical interpretation of this relaxation presents certain difficulties. Read and his followers claim Jacobson's *Progressive Relaxation*¹³ as the source of their ideas. But Jacobson states that the exercises advocated by Read's school are far removed from those developed by him. He objects to the very idea of "relaxation exercises," which implies a positive course of action comprising contraction followed by decontraction. According to him, his method consists of a "negative" process, a "not doing," which would clearly be incompatible with "positive" exercises.

For Helen Heardman,¹⁰ one of Read's followers, there are two kinds of relaxation, the one "mental," the other "physical," "conscious," or "specific." The former is equivalent to a mere state of rest between contractions. The latter consists of relaxation proper, or neuromuscular relaxation practiced during contractions. Mental relaxation occurs when the mind is at rest, while physical or conscious relaxation is accompanied by a high degree of mental

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concentration. Read and his followers, Thoms²⁰ and Goodrich,⁹ attach most importance to this latter form of relaxation. Moreover, they recommend that it should be used sparingly, when dilation is well advanced, since it is exhausting. Thus, we notice that relaxation is not as passive a phenomenon as it has generally been considered. It cannot be regarded as wholly active either, since, according to Heardman,¹⁰ specific relaxation practiced during pregnancy is not exhausting but invigorating. Some women even fall asleep during the exercises. Read himself has observed that this kind of relaxation can lead to states not far removed from unconsciousness, followed by amnesia on awakening. The question therefore remains highly complex.

It should also be mentioned that the German writer Prill²³ makes use of the English method by combining the Schultz²⁶ autogenous training with Read's relaxation. It is his opinion that autogenous training increases the analgesic effect and enables better results to be obtained than with Read's own method. His expectant mothers are not active but in a state of passive concentration.

Hypnotic methods

The overcoming of pain by hypnotic suggestion has been thoroughly established by experiment. Hypnotic suggestion methods were in use in obstetrical analgesia, especially in France, at the end of the last century, and in Germany about 1920 to 1923, and from 1923 have been in use in Russia, where they are still employed. They appeared in the United States about 1943 (Kroger) and have been developed since 1950, when interest in psychological analgesia was stimulated by the spread of Read's method (introduced about 1947). These applications, while all on a limited scale, have yielded a rich experimental harvest.

The word "relaxation" had not been mentioned before the introduction of these methods into the United States. American authors observed that relaxation included elements of hypnotic suggestion.^{19, 22} It

might therefore be regarded, in their opinion, as the equivalent of a light hypnotic state, "with increased suggestibility.*" Thus, certain authors,¹ starting from Read's technique, thought that if it "was carried a step further and a trance state induced, the results could be improved."

Read's Russian critics^{28, 32} also maintain that his "relaxation" is nothing but hypnotic suggestion.

At the present time hypnotic suggestion methods are in use in Russia,^{17, 33} either in their classic form, in which the kind of relaxation known as "relaxation-rest" acts as an introduction to a deeper trance, or in a form in which the "relaxation-rest" technique⁸ alone is employed. In the latter form, all the traditional procedures of hypnosis are avoided (authoritative suggestion, visual fixation, darkening of the room, etc.). In both cases, hypnotic states are induced in which suggestibility is increased. These are, in the author's terminology, mild inhibitory states favorable to the extinction of harmful and the implanting of helpful conditioned reflexes.

The psychoprophylactic method, or PPM (Velvovski)

The psychoprophylactic method described by the Soviet psychiatrist Velvovski³¹ in 1949 is a development of the hypnotic method which demonstrated the possibility of "verbal" analgesia. The new method attempts to do without hypnosis,† and the verbal influence operates through educative procedures.

Velvovski, like Read, starts from assumptions about the "painlessness" of uterine contractions, and the origins of the pain which comes to accompany them as a result of sociocultural factors. The mechanism in action is reflex-conditioned.

*Heardman¹⁰ had already emphasized that women are very much subject to suggestibility during the exercises practiced during preparation. In Read's book²⁴ there are descriptions of women "relaxed" during childbirth which suggest deep hypnotic states.

†Some Russian authors^{30, 36} consider that even with hypnosis eliminated, there still remains an important element of suggestion in PPM.

Pain must be prevented by educative procedures aimed at removing the causes. These procedures increase cortical tone and have a *prophylactic effect*. By contrast, hypnosis based on inhibition is essentially *curative* and by this very fact, irrelevant to PPM.*

Inhibitory procedures (hypnotic) were, however, only gradually rejected. During the early years of the application of the PPM, relaxation in the form of the "relaxation-rest" technique was employed with all prepared women. In these hypnoidal states (increased suggestibility), the effectiveness of the learning process was reinforced. About 1954, this procedure came to be reserved for difficult cases and, at the same time, purely local muscular relaxation (hands, abdomen, pelvis), independent of hypnoidal states, was recommended for all.

Psychoprophylactic method (Lamaze)

The Soviet psychoprophylactic method was introduced into France in 1952 by Lamaze and Vellay.^{20, 21} They adopted certain modifications, in particular introducing a form of relaxation, the application of which is entrusted to physiotherapists. This kind of relaxation is similar to that used by Read, and is called neuromuscular relaxation or education. It is probably derived from the "relaxation-rest" method, which was still in use in the U.S.S.R. for all women when Lamaze saw the method in action (1951).

On the theoretical level, the French exponents of PPM are careful to point out that relaxation does not work in the same way in their method as in Read's. They criticize Read's relaxation as leading to passivity, inhibitory states, and a lowering of the level of consciousness (although, of course, Read,²⁴ Thoms,²⁹ and Goodrich⁹ insist upon the *active* character of relaxation).

For the French school, relaxation is something *active* which will maintain and raise the threshold of cerebral sensitivity. But

some also express the view that "a state of muscular relaxation corresponds, neurologically, to an inhibitory state."²²

Comment

From this short account, it is clear that relaxation is employed to a greater or lesser extent in all methods, whether under the name of relaxation or under some other name. Unfortunately, there are no instruments which give an objective indication of the mechanism through which relaxation works. This mechanism therefore remains largely hypothetical, and, in consequence, the field is left open to very different and sometimes contradictory interpretations. For some, relaxation is something active, for others something passive. For some, it is accompanied by suggestion, for others it is independent of it.

To summarize, from what has been said relaxation may be thought of as having effects at three levels, (a) muscular, (b) central (attention), and (c) psychotherapeutic (interpersonal relations).

a. Muscular. There are no accurate and practicable instruments for measuring the degree of muscular relaxation.* Moreover, muscular relaxation has not been shown to be accompanied by analgesia. There are not enough detailed experiments in this field.

b. Central. It is not easy to draw a clear distinction between the peripheral and the central, but it is known that analgesia may be brought about by the mechanism of attention (e.g., the momentary insensitivity of the soldier wounded in the heat of action). This is, of course, the mechanism of concentration, distraction, diversion, or, in Pavlovian terms, of focusing upon a center of cortical activity. This mechanism is beginning to receive support from experiments on animals with modern electrophysiological techniques, in which it has been shown that, when a prepotent stimulus is presented (e.g., a mouse to a cat), there is inhibition

*Not all Russian authors share Velovski's ideas. This is not the place to enlarge upon the theory of PPM and the controversies which it has occasioned, but the reader may refer to the author's book.⁴

*Jacobson¹⁴ has described an "electroneuromyometric" instrument for measuring the degree of tension in a muscle, but so far this instrument does not appear to have been used by other investigators.

of messages from other sensory modalities at the more primary level.^{11, 15} Finally, recent neurophysiological studies of attention in human beings⁷⁻¹⁶ have provided an objective basis for the mechanism of *blocking* of nonprepotent stimuli during attention, at a subcortical level.*

c. Psychotherapeutic. As has been shown, certain Russian and American authors assign to relaxation a psychotherapeutic function through suggestion. The former express this in physiological terms (hypnoidal state with heightened suggestibility), the latter in psychological terms (interpersonal aspects of suggestion). Relaxation is practiced during preparation and during labor. In the former case, according to these authors the analgesic effect during labor occurs as a result of posthypnotic suggestion, in the latter by intrahypnotic effects.

True, in the learning process of relaxation the interpersonal relationship exists; but it would be exaggerated to assert that it is always a hypnotherapeutic relationship. A manifold set of relationships is possible. Besides, let us remember that in addition to the direct analgesic effect the psychotherapeutic process may have an indirect effect on sensitivity to pain: the psychotherapeutic relationship may have a psychosomatic effect on the physiological process of labor. In this way the "somatic" causes of pain may be lessened.†

It may now be asked how far the effects of relaxation at these 3 levels combine.

According to their theoretical outlooks, authors have concentrated upon one or other of these areas at the expense of the others. None of them appears sufficiently to have taken into consideration a decisive factor, the personality of the woman.

*These experiments may be a first step toward establishing a physiological basis for the mechanism of hypnotic suggestion which, according to Pavlov, depends upon inhibition induced by a focus of cortical excitation.

†Read²⁴ has already remarked upon the beneficial effect of the practice of relaxation on certain complications of pregnancy (vomiting, burning sensations in the stomach, etc.). The Russian authors report the same improvements after the practice of relaxation-rest. I have obtained good results with lumbar pains, using hypnoidal relaxation.

It is true that Read has tried to classify expectant mothers into several categories ("lazy and casual," "born mothers," "enthusiasts"). It is difficult, however, to see how these descriptions can correspond to fundamental personality types.

The Russian authors have tried to classify women according to their "nervous type." Pavlov identified four nervous types in animals (according to the strength and mobility of the process of excitation and inhibition of the cerebral cells and their balance). The strong, balanced, slow type (phlegmatic), the strong, balanced, quick type (sanguine), the strong, unbalanced type (choleric), and the weak type (melancholic). Suggestibility is a characteristic of the weak type. This classification, based originally upon animals, presents certain difficulties when it is transferred to human beings. The latter have a history which is important in the formation of their personality. Besides, there is no general agreement among Soviet authors on its applicability to expectant mothers. By studying personality some aspects of the history are taken into account by the Russian authors, but they consider only the conscious level, and this limits one's knowledge of personality. A thorough psychodynamic investigation takes into account unconscious factors as well. Very little research of this kind has been made with expectant mothers. Great methodological difficulties are involved in a study of this kind.

It may, however, be agreed that any woman can turn her experience of relaxation, passive or active, to good use only as it is integrated with her own personality, with its own affective development. Some will adopt the interpersonal level and analgesia will be attained through emotional channels. Others will use relaxation on a more "mechanical" level, in the form of concentration of attention upon some activity. Some women, moreover, may be able to turn to account both these two aspects, using the first during preparation and the second during labor.

Attempts have also been made to express

the beneficial effects of the interpersonal approach in terms of attention, within a psychoanalytic framework (transference). Margaret Brenman³ has advanced a tentative hypothesis here. She writes, of women delivered under hypnosis, ". . . the attention, if we may use that undefined concept, was directed to whatever the physician was doing and was so gratifying that possibly then the experience of pain was not so important any longer."*

It may be said, moreover, that to think in terms of activity versus passivity in the various methods is misguided. Activity and passivity are two states which almost always occur together. As has been indicated, according to Read, relaxation, considered as a state of "active" concentration leads to "passive" states of mind not far from unconsciousness.

It has not yet been demonstrated convincingly that EEG traces can provide objective indices of relaxation and hypnosis.† Kramarz and I⁵ have studied EEG records of subjects in a hypnotic state. In the majority of subjects, hypnosis failed to modify the tracing although, in the cases of some subjects, tracings were found which could not be interpreted simply. There were EEG records which might suggest modifications of the state of consciousness in either direction, toward hyper- or hypoactivity—slowing down of the EEG, suggesting a hypnagogic state; desynchronization of the alpha rhythm and accentuation of the ocular artefacts, suggesting increased vigilance.‡ Das and Gastaut⁶ with a Yogi found slow activity during the middle trance, but rapid

activity in the full trance state (concentration).

In conclusion, the way in which relaxation works in obstetrics is far from being explained. What must not be forgotten in practice, however, is that there is always, in varying degrees, a psychotherapeutic element in the practice of relaxation, involving the interpersonal relations between the expectant mother and the preparation team. Those who practice psychosomatic methods in obstetrics must be aware of this and see that good relations are established on the human level, during preparation, as well as in the labor room.

Summary

Relaxation is used in all the psychosomatic methods of obstetrical analgesia, hypnotic methods, natural childbirth, and the psychoprophylactic method. A critical analysis has been made of the theoretical foundations of relaxation in the various methods. These foundations are as yet very imperfectly elucidated. Three "levels" on which relaxation may operate are distinguished—muscular, central, and interpersonal. A woman may benefit from relaxation on one or more of these levels, according to her fundamental personality. A psychotherapeutic context is always involved, and this must be kept in mind by anyone using relaxation methods.

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*This state can be attained without loss of consciousness and even without hypnosis. Consider the following extract from an account by a young mother of her very recent labor: "From the moment the doctor entered the labor room, the intensity of the pains became markedly less, and when he told me to begin bearing down I felt no pain at all."²⁰

†Israel and Rohmer²² report similar tracings in autogenous relaxation (Schultz techniques) and in hypnotic relaxation.

‡After the diencephalon and the cortex, an attempt will certainly be made to locate the seat of hypnosis in the reticular formation. Svorad²⁷ has already advanced this hypothesis for animal hypnosis.

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Hematocolpos with imperforate hymen

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THE occurrence of the rarely observed gynecologic entity known as hematocolpos is interesting because of its apparent scarcity and the danger it may bring about.

Since Doyle's review of the literature in 1942,² in which he reported a total of 176 cases, isolated case reports have appeared which signify the rarity of this condition.

Etiology

The word "hematocolpos" is derived from the Greek words, *Hematos*, meaning blood, and *Kolpos*, meaning vagina.

In most cases of hematocolpos, one of 2 embryological abnormalities is the etiological factor responsible. The hymen, as it is being formed as the product of the combined embryological action of the urogenital sinus and the Müllerian ducts, may undergo certain abnormal changes which bring about its nonpatency. As the urogenital sinus advances upward like a diverticulum from outside, it envelopes the column of Müllerian cells which has already moved nearly four fifths of the distance from the cervix down to the vestibule. In most instances of the congenital anomaly known as imperforate hymen there is a persistence of a group of central epithelial cells in the membranes which ordinarily would have degenerated by the time of fetal maturity. Another congenital anomaly, as pointed out by Arey,¹ which may result in hematocolpos, is a non-patent vagina. Other less likely causes of this condition are inflammatory reactions during infancy or intrauterine life causing cicatrization of this area.

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The clinical and pathological processes which result from these congenital abnormalities produce certain definite findings which may be recognized shortly after menarche as hematocolpos, hematotrachelos, hematometra, hematosalpinx, and finally hemato-peritoneum.

Case report

In the last 25 years at St. Michael's Hospital, Toronto, we have encountered 4 cases which could be classified as hematocolpos due to an imperforate hymen.

The most recent case was that occurring in a 13-year-old girl who was perfectly well until July, 1959. At this time a gradual enlargement of the abdomen was noted.

Secondary sex characteristics, e.g., breast enlargement, had begun when the patient was 11 years of age (1957).

One month prior to admission the patient noticed urinary frequency which increased in severity until, by the time of entrance into the hospital, she would dribble during attempts at voiding.

Two weeks prior to admission to the hospital, Nov. 9, 1959, the patient gradually developed a dull aching pain in both lower quadrants of the abdomen. The pain was crampy and periodic, lasting 1 or 2 hours and then disappearing.

On admission to the hospital, Nov. 9, 1959, general physical examination revealed a well-developed girl of 13. The breasts and pubic hair indicated secondary sex characteristics had developed.

The abdomen showed the presence of an enlargement measuring the size of a 6 or 7 months' pregnancy (Fig. 1, C). It was a diffuse enlargement which transmitted a fluid thrill. A nodular hard area was present on the left superolateral area of the abdomen and this was thought to be the uterus in its displaced position. Vaginal

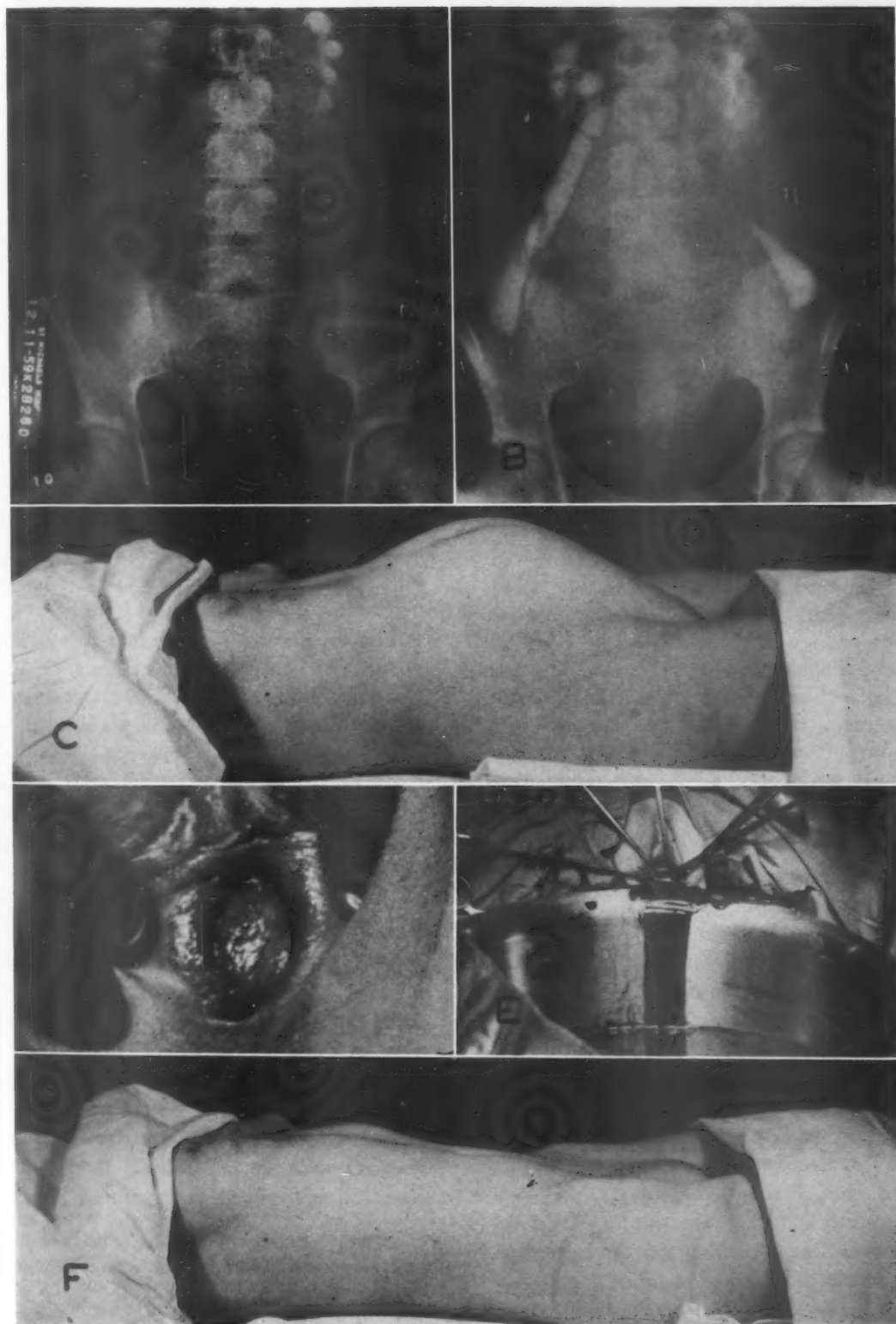


Fig. 1. *A*, Preoperative intravenous pyelogram showing bilateral hydronephrosis. *B*, Preoperative intravenous pyelogram showing bilateral hydroureters. *C*, Patient in operating room prior to drainage, showing marked abdominal distention due to imperforate hymen. *D*, Imperforate hymen, bulging forward, which at examination was quite bluish. *E*, Cruciate incision into imperforate hymen with drainage of 3,300 c.c. of chocolate-colored fluid. *F*, Appearance of abdomen, shortly after the evacuation of the fluid from the vagina.

examination revealed a tense bulging hymen, slightly bluish in color (Fig. 1, *D*). Rectal examination showed a bulging fluctuant mass passing down from the upper portions of the pelvis and encroaching on the rectum.

Laboratory investigations included a white blood count of 6,700. The hemoglobin 13.0 Gm. The sedimentation rate was 9 mm. in one hour.

The flat plate of the abdomen showed a mass arising from the pelvis and passing to above the level of the umbilicus. Intravenous pyelograms (Fig. 1, *A* and *B*) revealed markedly dilated ureters as well as bilateral hydronephrosis. No other congenital abnormality could be found.

At the time of operation, Nov. 13, 1959, a cruciate incision was made into the bulging hymen and 3,300 c.c. of chocolate-colored fluid was allowed to flow freely from the distended vagina (Fig. 1, *E*). The uterus and adnexa could be felt returning to the pelvis from their temporary site in the abdomen and the abdomen returned to its normal size (Fig. 1, *F*). Culture of the fluid failed to grow any organisms.

The postoperative course was entirely uneventful and afebrile. Prophylactic antibiotic therapy was started postoperatively to offset the possibility of any infection in the ideal culture medium provided by the old blood. The patient was discharged from the hospital feeling quite well and resumed her school duties a few days later.

Repeat pyelograms will probably be carried out in the future to follow the condition of the ureters and kidneys.

Comment

One of the rarer gynecological entities is an imperforate hymen with the establishment of a back pressure system on both the genital and urinary systems.

The involvement of the genital organs, due to the retained menstrual flow, will vary according to the amount of blood retained and also depending on the distention of the uterus and Fallopian tubes.

Most cases, just like the present one, show displacement of the normal uterus to a perching position at the top of the distended vagina.

The symptoms of the condition will vary quite considerably, depending on the amount

of blood retained and the encroachment on the surrounding organs. Rather commonly, besides the absence of menstruation, the patient is unable to void or else she dribbles, as a result of direct displacement of the bladder.

The signs of hematocolpos which are pathognomonic of the condition include a bulging imperforate hymen, with its characteristic bluish discoloration and a fluctuating cul-de-sac mass.

The establishment of the presence or absence of other genitourinary abnormalities is quite desirable. Investigations on the urinary tract can be readily carried out by means of cystoscopic examinations of the bladder and intravenous pyelograms. These studies may reveal other pathological changes brought about by the distention of the genital organs. Other unrecognized congenital defects may occasionally be found.

The treatment of hematocolpos involves incising the imperforate hymen. This may be done by means of a simple cruciate incision. Some prefer hymenectomy because of the unlikelihood of future agglutination of the hymenal edges. This was carried out in 1 of our 4 cases. Even distention of the uterus and tubes will be cured by this simple procedure. Very rarely will laparotomy be required because of incomplete drainage.

Summary

A case of hematocolpos occurring in a 13-year-old girl has been presented. Of interest was the large amount of retained blood which measured 3,300 c.c. Back pressure effects of the urinary system were demonstrated. Cruciate incision provided adequate drainage. Normal resumption of activity followed an uneventful postoperative course.

I wish to thank Dr. D. E. Cannell for his interest in this case and Mr. Arthur Smialowski for his excellent photographs.

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Observations of the steady state of lactic dehydrogenase activity across the human placental membrane

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STUDIES, so far reported, attempting to define the serum activity of lactic dehydrogenase (LDH) in the altered physiologic states of pregnancy and growth indicate that the activity of this enzyme is higher in fetal than in maternal serum.¹⁻³ Several mechanisms for the maintenance of this differential across the human placental barrier exist.

In view of the concentration gradient present, placental transport of intact LDH from mother to baby by the mechanism of diffusion would seem unlikely. However, studies limited to a comparison of activity of this enzyme in sera obtained from the maternal vein and fetal cord may not necessarily depict the exact circumstances at the placental site. The possibility that the

placenta could be a significant source for fetal LDH is suggested by observation that this enzyme is liberated from infarcted tissues,⁴⁻⁷ a process the placenta is reported to undergo during its senescence.^{8,9}

Another explanation might be active transport. During recent years the concept has grown that the placenta must possess active secretory mechanisms capable of effecting transport across the membrane despite a diffusion gradient in the opposite direction.⁸⁻¹⁵ Such a process is suggested as the mode of transport for many substances, such as L-histidine¹⁴ and ascorbic acid,^{10,11} which are found in higher concentrations in fetal than in maternal blood, a circumstance identical with that reported for lactic dehydrogenase.

Still another possibility exists. The serum enzyme levels of baby and mother may be completely independent of each other. The higher level observed in fetal serum may be a reflection of the cellular proliferation associated with fetal growth since rapidly growing, highly glycolytic tissue is known to be associated with an increased activity of this enzyme.¹⁰⁻¹⁸

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The present study was undertaken to investigate the steady state of lactic dehydrogenase between maternal and fetal organisms in an endeavor to determine the mechanism for the maintenance of the differential activity across the human placental barrier for this protein moiety.

Methods

Venous blood was obtained from non-pregnant subjects and from gravid women during the course of pregnancy, delivery, and puerperium. At delivery, blood samples were drawn from the maternal brachial artery and the intervillous space. The latter samples were collected by transabdominal aspiration.¹⁹ Immediately following delivery of the baby, umbilical arterial and venous samples were drawn.

Independently of the analyses and prior to compilation of the data, each pregnancy was classified as normal or toxic according to the criteria established by the American Committee on Maternal Welfare.²⁰

In order to minimize the error incident to hemolysis of enzyme-rich erythrocytes, all samples were collected with extreme precaution. Nineteen-gauge needles were used. Needles and syringes were siliconized. Immediately after sampling, the blood was placed in siliconized and heparinized tubes contained in a plastic ice chamber. Blood samples were centrifuged at 4° C., the plasma separated, and frozen. Samples in which hemolysis was visible were not included in the analysis. The error incident to hemolysis was further controlled by determining the hemoglobin concentration of the samples.²¹ LDH activity in different dilutions of hemolysates gave a range of 32 to 88 units per milligram of hemoglobin. Therefore, hemolysis releasing 15 mg. of hemoglobin into 100 ml. of plasma would raise its LDH activity by 5 to 13 units per ml.²² Since the amount of LDH added to the plasma by this degree of hemolysis is within the limits of the method, we elected to include only samples in which the hemo-

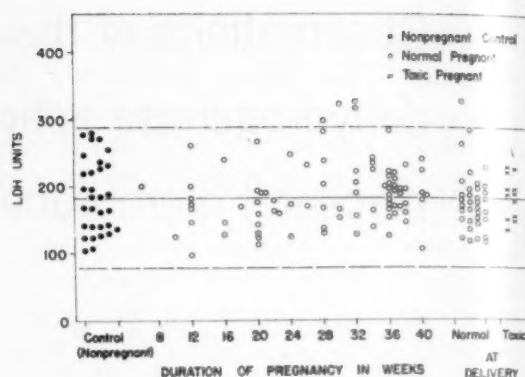


Fig. 1. LDH activity in maternal venous plasma during pregnancy and at delivery. Solid line depicts the mean LDH activity for nonpregnant control group, dotted lines are placed at 2 standard deviations from this mean.

globin concentration was less than 15 mg. per cent.

The lactic dehydrogenase activities of the various plasma specimens were determined at a temperature of 24° to 26° C. according to the spectrophotometric method of Wroblewski and LaDue.²³ In this technique, the rate of change in optical density at 340 μ due to the oxidation of reduced diphosphopyridine nucleotide (DPNH) is utilized to measure the LDH activity of the sample. The activity is expressed as units per milliliter of plasma per minute. One unit is equal to a decrease in optical density of 0.001 per minute per milliliter.

All determinations were in duplicate.

Results

In the scattergram (Fig. 1), the activity of lactic dehydrogenase measured in plasma obtained from the antecubital vein of 31 healthy, nongravid subjects (182 ± 52 units) is compared to that present during the course of pregnancy (188 ± 49 units) and at the termination of the second stage of normal (179 ± 46 units) and toxic labor (184 ± 32 units). Statistical analysis of the data demonstrates that the maternal venous plasma activity of this enzyme is not altered by the physiologic processes of pregnancy and labor or by the pathologic state of pre-eclampsia-eclampsia.

In Table I, the LDH activities of plasma samples from the various sites at the termination of labor are shown. Because of the marked variation in plasma LDH activities from individual to individual coupled with inability to obtain adequate samples free of significant hemolysis from each site in every instance, we elected to compare the LDH activities of the various samplings with that present in the maternal arterial plasma. The calculated mean ratios are depicted. In addition, any statistical deviation of this value from unity is indicated.

The comparison of enzyme activity in plasma obtained from the maternal vein to that present in maternal arterial plasma yielded a ratio of 0.99 ± 0.12 in normal labor, and of 0.99 ± 0.08 in toxic labor. These values do not differ statistically from unity, indicating that the maternal arterial and venous plasmas contain comparable LDH activities. Furthermore, these ratios do not differ from each other.

The plasma from the intervillous space, however, yielded slightly greater enzyme activity than the corresponding maternal arterial plasma. In normal labor, a ratio of 1.22 with a standard deviation of ± 0.25 was established. This value differs from 1.0 at the 2 per cent confidence level. In toxic labor, a comparable ratio was established

(1.29 ± 0.40). However, this value does not deviate significantly from unity, perhaps referable to the paucity of samples comprising the mean.

The ratios obtained in both normal (2.04 ± 0.54) and toxic (2.06 ± 0.61) gestations by comparing the activity of the enzyme in plasma in the umbilical vein with that in the maternal artery differ significantly from unity. Similar ratios were obtained (1.97 ± 0.58) in normal and (1.90 ± 0.51) in toxic pregnancies by comparing the activity of lactic dehydrogenase in umbilical arterial with maternal arterial plasmas. These ratios indicate that, on the average, baby plasma has twice the LDH activity of maternal plasma.

In Table II, the individual enzyme levels are depicted in the 10 instances during the study in which it was possible to obtain adequate samples free of significant hemolysis from the various sites. Six of these complete sets were obtained at the termination of the second stage of normal pregnancy, and 4 were obtained during the interval of birth from a toxic mother.

The activity of the enzyme in the umbilical arterial plasma sample was compared with that in plasma obtained from the umbilical vein in the 34 instances in which adequate samples for analysis were collected from

Table I. Ratio of plasma LDH activity in various sites compared with maternal arterial plasma activity*

Ratio	Normal pregnancy at delivery				Toxic pregnancy at delivery			
	No. of comparisons	Mean ratio	S. D.	Significance†	No. of comparisons	Mean ratio	S. D.	Significance†
M. V. M. A.	33	0.99	± 0.12	None	11	0.99	± 0.08	None
Ivs. M. A.	11	1.22	± 0.25	S. S.	4	1.29	± 0.40	None
U. V. M. A.	34	2.04	± 0.54	H. S.	11	2.05	± 0.61	H. S.
U. A. M. A.	24	1.97	± 0.58	H. S.	8	1.90	± 0.51	H. S.

*Mean maternal plasma LDH activity is 179 ± 40 units in normal and 191 ± 31 units in toxic pregnant groups.

†Significance of deviation of the mean ratio from unity. S. S., significant at 2 per cent level; H. S., highly significant; M. V., maternal vein; M. A., maternal artery; Ivs., intervillous space; U. V., umbilical vein; U. A., umbilical artery.

Table II. Plasma LDH activities in the 10 instances at delivery in which complete sets of samples were available for analysis*

Classification of pregnancy	Mother		Baby		Intervillous space
	Artery	Vein	Artery	Vein	
Normal	238	263	400	493	238
	153	165	387	334	180
	213	227	417	454	298
	153	136	415	372	193
	176	183	476	395	211
	159	121	415	434	181
Mean	182	183	418	414	217
Toxic	208	227	333	400	217
	216	222	420	400	233
	133	150	356	412	150
	198	189	281	294	374
Mean	189	197	348	377	244

*Each value is an expression of LDH activity in units per milliliter per minute.

both vessels (Fig. 2). The ratio established by this comparison in 25 cases of uncomplicated pregnancy was 0.98 ± 0.11 . Statistical analysis demonstrates that this ratio does not deviate significantly from unity, indicating that in normal pregnancy the plasma LDH activity is identical within the limits of the method in both sites. In pregnancy complicated by the toxic state (9 cases), the ratio established by this comparison had an arithmetic mean of 0.88 with a standard deviation of ± 0.09 . This ratio does differ significantly from 1.0, indicating that in toxic gestation the plasma activity of lactic dehydrogenase is not identical in the 2 sampling sites.

In Fig. 3, the plasma LDH activity in the umbilical vein has been plotted against the corresponding activity present in the maternal arterial sample. The scatter indicates that there is no direct relationship between the 2 samples.

The plasma activity of lactic dehydrogenase was followed in 16 mothers during the puerperium. The enzyme activity of each postpartum sample was compared with that present in the specimen collected at delivery. In Fig. 4, the mean ratio for each interval is depicted. The deviation of the ratio from 1.0 indicates that there is a significant increase in maternal plasma LDH activity following parturition.

Comment

The data demonstrate that pregnancy is not associated with any significant alteration in the activity of lactic dehydrogenase as measured in plasma obtained from the antecubital vein. This circumstance is true regardless of the stage of pregnancy, the occurrence of labor, or the presence of the toxic state. During the puerperium, however, there is a rise in maternal plasma LDH activity.

The fact that the plasma activity of lactic dehydrogenase remains constant during the latter weeks of pregnancy, an interval of decreasing plasma volume, suggests that there is a "clearance" mechanism²⁴ within the maternal organism for this enzyme. The rise in enzyme activity and prompt return to pre-existing levels noted during the puerperium might be a reflection of this process disturbed briefly by the postpartum diuresis. An alternative explanation would be the liberation of the enzyme from "involuting" tissues.

The data obtained from the group of patients studied at delivery indicate that the enzyme activity measured by following the change in optical density due to the oxidation of DPNH occurs at a faster rate in fetal than in maternal plasma. The possibility that this differential in activity across the placental membrane could be due to the

transport of lactic dehydrogenase as an intact moiety from mother to baby is not supported by the data. The mechanism of diffusion is ruled out by observation that the maternal placental pool does not constitute a rich, localized source of LDH globulins. The mechanism of active transport is unlikely since maternal plasma withdrawn from the intervillous space does not contain less activity than the plasma sample obtained from the maternal arterial bed.

The fact that neither of these mechanisms is in operation in normal pregnancy is further indicated by the observation that fetal plasma leaving the fetal surface of the placental membrane via the umbilical vein displays the same degree of LDH activity as the plasma entering the fetal placental capillary network via the umbilical artery. This circumstance also rules out any significant addition of LDH globulins to the fetal plasma by the placenta through the process of synthesis or as a result of placental necrosis.

In toxic gestation, however, the ratio, 0.88 ± 0.09 , established by comparing the enzyme activity in umbilical arterial plasma with that in umbilical venous plasma does differ significantly from 1.0. This circumstance, coupled with inability to detect any loss in maternal plasma activity during the latter's transit through the placental pool, suggests that, in the toxic state, LDH globulins are added to fetal plasma by the fetal placental tissue, perhaps by the mechanism of infarction.

Since the present study denies any placental transport of lactic dehydrogenase from mother to baby and rules out, at least in normal gestation, any significant contribution by placental synthesis, the conclusion is that the fetus must build this protein complex from precursors. According to this view, the level of enzyme activity of fetal plasma would be determined by factors not necessarily related to those determining the maternal level. The results depicted in Fig. 3 demonstrate that there is no direct relationship between the plasma LDH activities observed in umbilical venous samples as

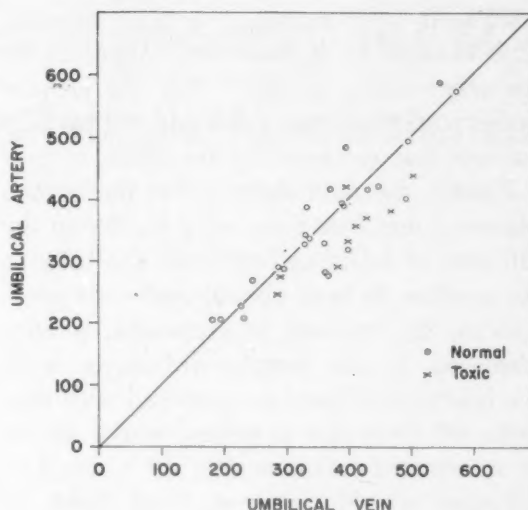


Fig. 2. Comparison of LDH activity in umbilical artery and umbilical vein plasmas. LDH activities in the 2 umbilical vessels are expressed in units per milliliter per minute. Diagonal solid line represents the theoretical curve for identical LDH activities in the 2 sampling sites.

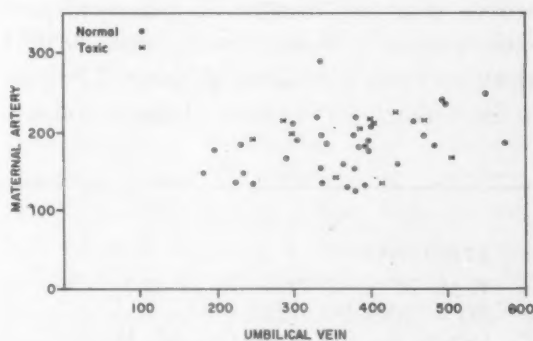


Fig. 3. Relationship of plasma LDH activity between mother and newborn. Maternal arterial and umbilical venous LDH activities are expressed in units per milliliter of plasma per minute.

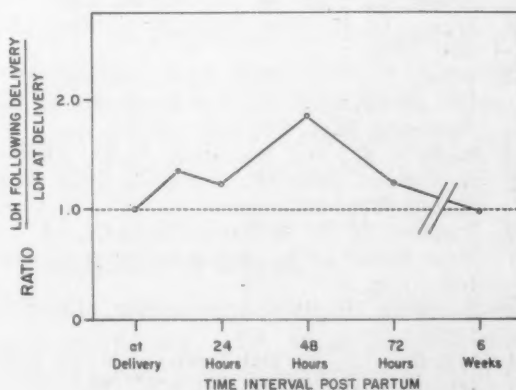


Fig. 4. Plasma LDH activity of 16 mothers post partum.

compared with maternal arterial samples. This concept is, furthermore, supported by the observations of Hill¹⁷ that the enzyme activity throughout childhood (growth?) exceeds that recorded for the adult.

Finally, the data suggest that the human placental membrane acts as a barrier to the diffusion of LDH activity from the baby to the mother. In both normal and toxic pregnancies, the increase in enzymatic activity displayed in the sample withdrawn from the intervillous space as compared with that collected from the maternal artery might be interpreted as supporting the concept of diffusion of this enzyme from baby to mother. However, any significant addition of LDH globulins to the placental pool plasma by the fetus would necessarily be reflected as a decrease in activity in umbilical vein as compared with umbilical arterial plasmas. Since this was not observed, we believe that any increase in placental pool activity must represent the addition of LDH globulins from the placental tissue. The possibility that, in human beings, minute

amounts of lactic dehydrogenase may diffuse across the placental barrier from baby to mother cannot be ruled out by this study.

Conclusions

1. The physiologic processes of pregnancy and labor, as well as the pathologic state of pre-eclampsia-eclampsia, are not associated with any alteration in maternal plasma activity of lactic dehydrogenase.
2. The higher level of enzyme activity present in fetal as compared with maternal plasma is not a consequence of placental transport of intact LDH globulins from maternal to fetal organism.
3. The human placental membrane acts as a barrier to the diffusion of LDH globulins from fetus to mother.
4. In toxic gestation, umbilical vein plasma displays greater activity than umbilical arterial plasma, perhaps as a result of placental infarction.

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Criteria by which toxemia of pregnancy may be diagnosed from unlabeled formalin-fixed placentas

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ALTHOUGH the criteria characterizing acute and subacute placental infarction have been repeatedly illustrated and described in previous articles¹⁻⁵ and their significance to pre-eclampsia, eclampsia, and abruptio placentae pointed out, there continues to be much skepticism not only as to their existence but also as to how these lesions could conceivably produce toxemia of pregnancy.

There is general agreement that the placenta is indispensable to the occurrence of toxemia. If so, it must elaborate some identifiable substances, or show pathologic changes such as characterize disease in other organs, which could logically produce the manifestations of this disease.

Failure of many investigators to verify these pathologic changes in placentas from patients with toxemia may be attributed to examining the specimen in its fresh state. It should not be examined until it has been fixed in 10 per cent formalin for 4 to 6 weeks or, if need be, as late as 2 to 3 months after delivery. Correct diagnosis, although possible, is much more difficult in freshly delivered placentas because of concealment of the

lesions by excess blood and the extreme difficulty of cutting the very soft tissue.

It is solely on account of the importance of this knowledge that we desire to present the criteria by which a correct diagnosis of pre-eclampsia, eclampsia, and abruptio placentae may be made on unlabeled placentas. One would hardly essay to subject himself to such a test (as has been carried out in several obstetric centers) unless the placental abnormality is actually present and trustworthy.

For this reason it is desired not only to restate previously proved criteria, but to mention some additional ones more recently discovered in the hope that other clinics will put them to the test for their specificity for toxemia of pregnancy. An abundance of illustrations, both gross and microscopic, may be found in previous publications,¹⁻⁵ particularly that of Bartholomew and Colvin.² It will be necessary to reproduce some of them to prove the criteria adequately.

Designation of infarcts

In the early years of study of placental abnormality only the most striking and obvious lesions were recognized. For want of meaningful terms, the white infarcts were termed "A," the yellow, "B," and the yellow-

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brown, "C," following the example set by the vitamins. It was soon realized that these were of slow development, had villus capillaries of normal size, and showed no relation to toxemia.

Later on it was found that infarcts of a brown color, termed "D" lesions, were associated with toxemia of several weeks' duration. Sometime later, it became apparent that in the placentas in acute and subacute toxemia of pregnancy there were areas of dark to black color, respectively, sharply demarcated from adjoining light gray normal placental tissue (Fig. 1). Occasionally, the involvement was so extensive (Fig. 2) that there was very little normal tissue left to furnish contrast. This was particularly true in fulminating abruptio placentae. These lesions were termed "early E" (the more acute) and "late E" (the subacute). The basis for differentiation of dark "early E" and black "late E" will be explained later. It is believed that the "early E" and "late E" infarctions are the types most commonly overlooked. They were first recognized by Young,⁶ and later confirmed by Bartholomew and Kracke,¹ Bartholomew and Colvin,² Patterson and co-workers,⁷ Falkiner and Apthorp,⁸ Steigrad,⁹ and Thomsen.¹⁰ It also became apparent to us that the placental abnormality of eclampsia and abruptio placentae was identical both grossly and microscopically.

During these years of observation, several other types of lesions were recognized, often

associated with toxemia but not concerned with the etiology itself, namely, "F," appearing as an excavated or empty space; "G," appearing as a coagulum of red, brown, or white color according to age of the clot, and "H," a semitransparent gelatinous partial coagulum. Each of these represents a mixture of maternal and fetal blood, apparently due to a ruptured villus capillary. In lieu of more meaningful descriptive designations, the alphabetic labels have remained in use.

Preparation of the placenta for fixation

At the time of expulsion of the placenta, if circumstances permit, the presence or absence of localized or generalized constrictions of the fetal placental arteries and veins should be noted. They appear to be more numerous in cases of ante- or intrapartum toxemia.

1. The membranes should be trimmed from the margin of the placenta except at the site of any clot of considerable size which spreads out and is adherent to the under side of the membranes, and which represents a possible ruptured marginal sinus as opposed to hemorrhage at the site of a marginal infarction of the placenta.

2. Any film of lightly adherent blood on the maternal surface should be brushed away, but one should avoid disturbing any firm clot imbedded in the substance of the placenta (abruptio).

3. Each placenta should be tagged with hospital record number and date, printed

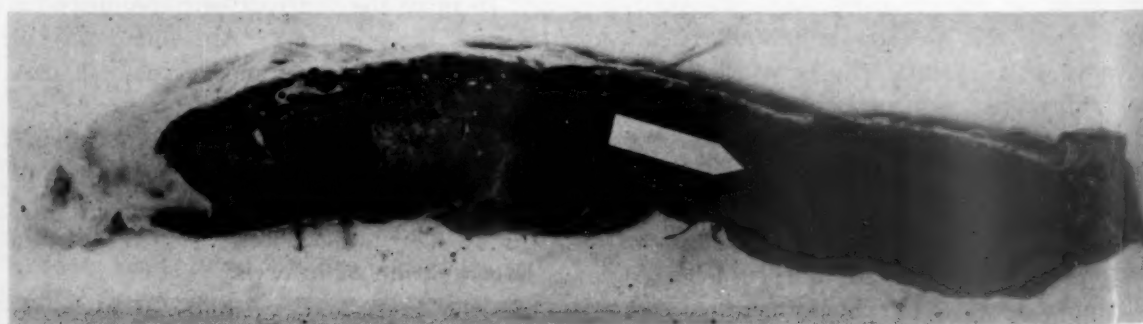


Fig. 1A. Strip of formalin-fixed placenta from a case of acute toxemia which developed during labor. Urine and blood pressure were normal on admission early in labor. Blood pressure 116/90, proteinuria flocculent at delivery. The black portion represents extensive "early E" infarction. Effect on blood pressure and urine only transient. Earlier development would have produced severe toxemia.

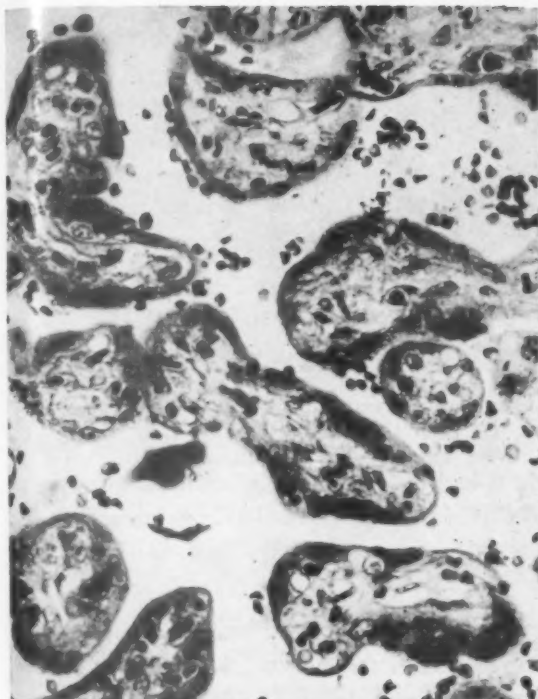


Fig. 1B. Microscopically, the light normal portion of the placenta shows open intervillous spaces, villi of normal size, villus capillaries of normal size (width of 1 to 3 red cells), and light-staining intact nuclei of chorionic epithelium.

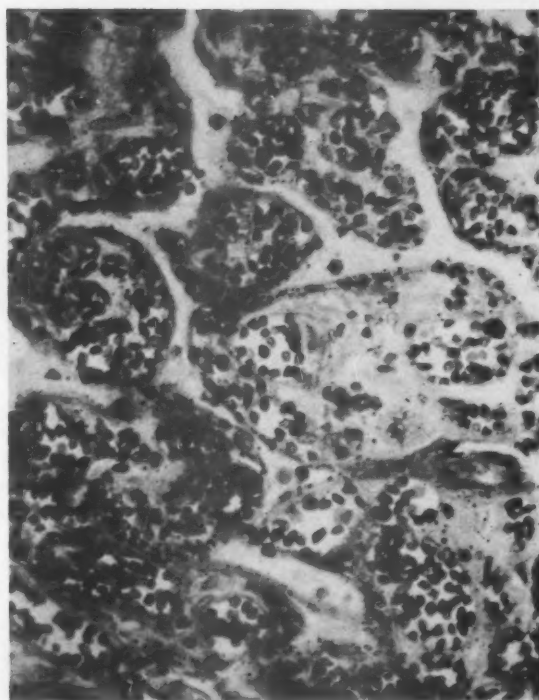


Fig. 1C. The black acute "early E" infarcted portion shows narrow to obliterated intervillous spaces, due to enlarged crowded villi, secondary to distention of villus capillaries (width of 10 to 20 red cells), and dark-staining (pyknotic) fragmenting (karyorrhexic) nuclei of chorionic epithelium.

with pencil, tied to the short stump of cord. Omit the name and the clinical diagnosis to insure objectivity in examination.

4. The placenta should be immersed in a large crock containing sufficient 10 per cent formalin to cover the specimen completely. It should lie flat and not be folded or kinked upon itself.

5. To furnish controls, the fifth placenta, and each multiple thereof, should be obtained from a nontoxic patient, i.e., without ante-, intra-, or postpartum proteinuria or hypertension (135/85 or more).⁴

6. A description of the gross findings of each placenta should be recorded and made a part of the case record.

Inspection of the fixed placenta before cutting

Fetal surface.

1. Note the localized areas of unusual thickness, which suggest infarction, espe-

cially if dark. The reason for this will be mentioned subsequently.

2. Note the localized or elongated spasms of placental arteries or veins and whether they are few or many.

Maternal surface.

1. If the entire surface is of dark or black color, this is strongly suggestive of massive infarction. The reason for this will be discussed later.

2. Areas of dark or black color (infarcted) may appear interspersed with areas of light gray color (normal), and suggest localized acute infarctions.

3. Firm, black or brown clots imbedded in the substance of the placenta usually indicate the effect of thromboplastin on blood in decidual spaces as in abruptio placentae.

Gross examination of cut strips

Acute "early E" infarction may be massive, involving most or all of each strip (Fig. 2)

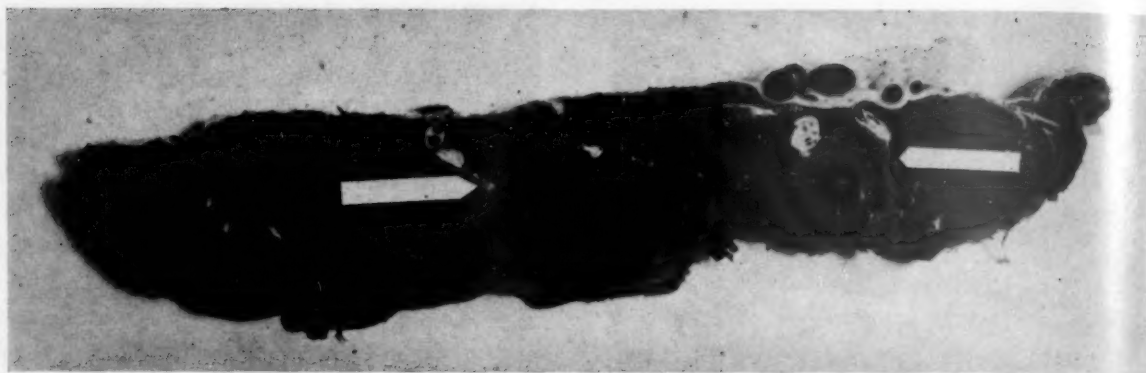


Fig. 2A. Strip of placenta from a case of superimposed fulminating severe abruptio placentae involving entire strip, except at extreme right, with acute "E" infarction. Blood pressure near term 135/85, proteinuria, a trace. Twelve hours later, severe hemorrhage, abdominal pain, and rigidity of uterus, blood pressure 160/100, proteinuria flocculent, and shock. Spontaneous rapid labor, stillborn baby, 2,000 c.c. blood loss; transfusions given, recovery.

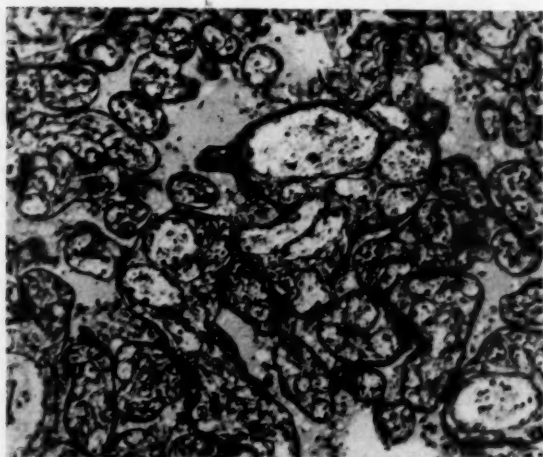


Fig. 2B. Microscopically, distended capillaries causing enlargement and crowding of villi, narrowing or obliteration of intervillous spaces, anoxic necrosis of chorionic epithelium, thromboplastin-induced intervillous and subplacental thrombosis, forming large clots and causing abruptio placentae. Arrows point to compact "late E" infarction. What process other than placental vein sphincter spasm could have triggered this sudden change?

which is more typical of abruptio placentae or intrapartum toxemia. It is of dark color. It may also be localized, involving several strips in succession, or appear as separate dark areas which are more typical of pre-eclampsia or eclampsia.

Massive "early E" infarction (Fig. 3) develops intra partum in about 10 per cent of patients free of hypertension and proteinuria on admission in labor, but who show heavy

proteinuria at delivery and also postpartum hypertension for 12 to 24 hours.⁴ It is also seen occasionally in hypertensive vascular disease with gradual antepartum rise in blood pressure late in pregnancy but with little or no proteinuria until a sharp rise in blood pressure occurs along with very heavy proteinuria (superimposed toxemia) necessitating prompt induction of labor. Acute infarction may be "early E" (slightly firm, still spongy), or "late E" (firm, compact, and shiny), and of slightly longer duration (few hours).

Massive "acute E" infarction, when arising late in pregnancy, is almost certain to be associated with abruptio placentae or eclampsia unless labor is promptly induced. If it develops intra partum, the patient usually is delivered before abruptio placentae or eclampsia occurs.

Characteristics of and reasons for acute "early E" infarction

1. Why is the "early" and "late E" infarction dark to black? The microscopic appearance of the villi indicates that exit of fetal blood from the involved placental unit(s) has been obstructed by spasm of the corresponding placental vein sphincter(s) (Fig. 4). The fetal heart continues to force blood into the units. As a result the villus capillaries become greatly distended (Fig 5B)

causing the villi to be stretched, greatly enlarged, and crowded. The intervillous spaces consequently are narrowed or obliterated, depriving the chorionic epithelium of maternal blood. Anoxic necrosis rapidly develops as evidenced by breakdown of the nuclei, which will be described later.

An early product of necrosis of chorionic epithelium is thromboplastin which is particularly abundant in placental tissue. It must reach the general circulation and set up widespread intravascular fibrination even before localized thrombosis closes the intervillous spaces of the involved tissue (Fig. 5B). Thrombosed blood is dark, or black, and produces the color change in the infarcted area.

In law, a phrase, *res ipsa loquitur*, is used, which means the evidence speaks for itself. It is equally applicable to the pathologic condition described above, for it is inconceivable that the appearance could be explained in any other way.

2. Intervillous thrombosis in "early E" infarction is apparently not uniformly advanced in all portions of the infarcted area; hence, fixation fluid can penetrate some of the intervillous spaces and can be squeezed out of the tissue when pressure from side to side is applied.

3. The involved area of infarction,

whether localized or extensive, is thicker than the surrounding noninfarcted tissue. This is obviously due to excessive enlargement of the individual villi, resulting from distention of villus capillaries (Figs. 1, 2, and 5).

4. The "early E" infarcted area is slightly firmer than the adjoining normal tissue because of partial intervillous thrombosis, which still permits the infarct to bend without breaking nearly as well as the adjoining normal tissue.

5. The moistened surface of the "early E" infarct presents a stippled appearance (Fig. 6) since the individual villi are only partly encased in thrombosed intervillous blood, permitting them to project individually from the cut surface and appear as "high lights."

6. A fairly sharp line of demarcation is seen where "early E" infarction adjoins normal placental tissue (dark, bordering on light gray) (Fig. 6). This proves that the infarction is initiated in and follows the pattern of the fetal part of the dual circulation which contains the placental vein sphincters. The congestion present in the area of infarction is that of distended villus capillaries, the maternal intervillous circulation actually being diminished as the result of enlargement and crowding of the villi.

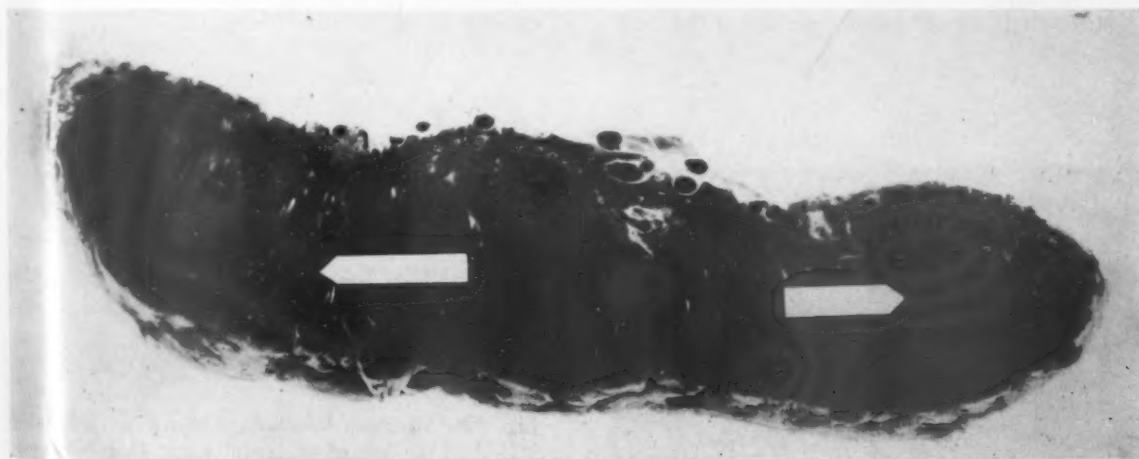


Fig. 3. Placental strip from case of intrapartum toxemia. The patient developed heavy proteinuria during labor and complete "late E" infarction. Arrows point to compact thrombosed areas identical grossly and microscopically with those in Fig. 2A. These areas reflect light when moistened and rubbed lightly and do not exude fixation fluid.

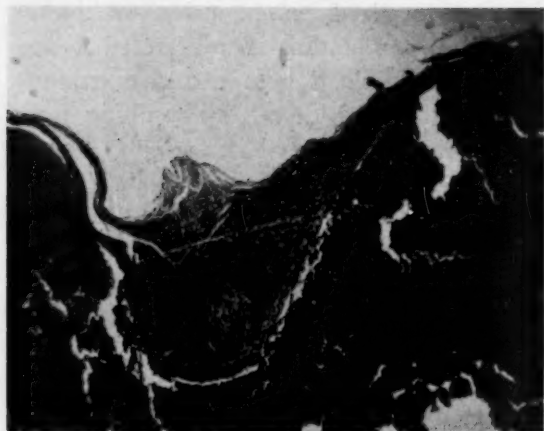


Fig. 4. Placental vein sphincter, recognized externally by sharply localized constriction in vein. Sphincter exhibits a central thick core of smooth circular muscle fibers cut transversely and a thin layer of longitudinal smooth muscle fibers adjoining the blood stream. Obviously, it is possible that contraction of this sphincter induced by a spasmogenic agent could readily obstruct exit of blood from its corresponding placental unit and produce the villus changes resulting in necrosis and thrombosis locally and distantly.

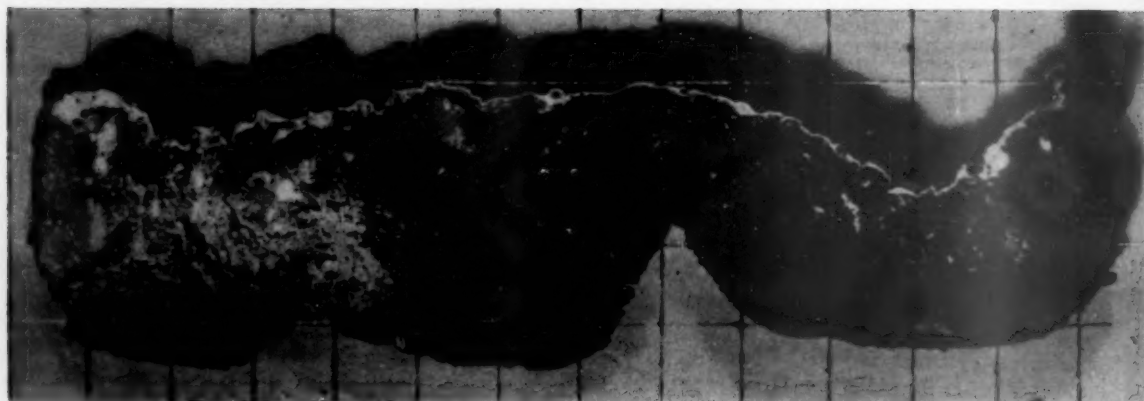


Fig. 5A. Strip of placental tissue, the black spongy-appearing acute "early E" infarction involving most of the placenta, leaving about one third unaffected. There is a sharp line of demarcation separating the light-colored normal tissue from the dark infarcted portion. Intrapartum acute massive abruptio placenta at term. Intrauterine fetal death; severe hemorrhage; recovery.

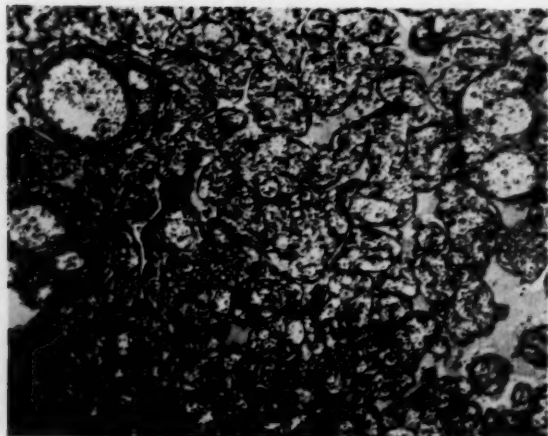


Fig. 5B. Microscopic appearance of dark acutely infarcted portion of placental strip. Distended enlarged villus capillaries cause enlargement and crowding of villi, inadequate intervillous space, anoxic necrosis of chorionic epithelium, production of thromboplastin, and fibrin deposition in intervillous spaces.



Fig. 6. Strip of placental tissue from a case of acute severe abruptio placentae shows extensive involvement with "early E" infarction. About one fourth of the placenta is of light normal color within which there is a small area of early infarction. The infarcted area was fairly soft, exuded fixation fluid on side-to-side pressure, and shows the bright stippled high lights of villus projections as yet incompletely involved by intervillous thrombosis.

Characteristics of "late E" infarction

1. The consistency is uniformly firm because of generalized, more advanced intervillous thrombosis throughout the infarcted area.

2. It is more homogeneous; therefore, the area of infarction resists bending of the strip. As a result, it breaks away along the border where the normal and the "late E" infarcted tissue join.

3. Like the "early E," the "late E" type is thicker than the adjoining normal tissue.

4. If one moistens and lightly rubs the surface of the infarction with the finger tip, holding the strip obliquely toward the light, the infarcted area will reflect the light as though it were a glazed or mirrored surface (Figs. 2, 3). This is due to uniformly throm-

bosed intervillous blood and indicates an infarction of slightly longer duration or of more rapid development than the "early E." There is no stippled appearance as in the "early E."

5. Fixation fluid cannot be squeezed out of the infarcted area, since it has already been excluded by more complete preceding intervillous thrombosis.

6. The dark to black color of the infarct is increased and more sharply demarcated. "Late E" infarction indicates an infarction of somewhat longer duration or more rapid development than the "early E," but cannot be expressed in exact units of time. It is based mainly upon the degree of change in the nuclei of the chorionic epithelium and the more advanced degree of thrombosis.



Fig. 7. Strip of placental tissue from a case of abruptio placentae showing area of compact "late E" infarction, previously compressed by an underlying firm clot. Infarcted area is firm, compact, and shiny. It did not exude fixation fluid when compressed, because of previous complete intervillous thrombosis.

Characteristics of the "D" infarction

The "D" infarct is of a light chocolate-brown color, as a result of further breakdown of the hemoglobin of the villus and intervillous thrombosed blood. It represents a later stage of "late E." Since labor must often be induced before infarction can progress to this stage, the "D" infarct is not seen as often as the earlier types, except in clinics receiving neglected patients.

"Late E" and "D" infarcts very often show small punctate hemorrhages in their substance, evidently the result of rupture of overdistended villus capillaries. The blood is black and firmly coagulated. These clots may vary from 1 mm. to several centimeters in size, and from black to brown to yellow or white, according to age. They often show striations due to layering of the fibrin.

The "D" infarct is present in severe grades of pre-eclampsia, eclampsia, and abruptio placentae. In the latter, very firm black or brown clots are often found, deeply imbedded in the placental substance. They subtend a compressed area of infarction (Fig. 7) which apparently is the source of thromboplastin which initiates the clotting process. The consistency of this finding inclines one to this explanation of the hemorrhage rather than to rupture of an atherosclerotic spiral artery.

Significance of nuclear changes in the chorionic epithelium in relation to the duration of toxemia

1. Healthy chorionic nuclei are round and present a pale, somewhat stippled, appearance. Injury from anoxia causes the nuclei to acquire an increased affinity for the hematoxylin nuclear stain. They become intensely dark, almost black, and are then said to be pyknotic.

Pyknosis is occasionally seen in normal placental tissue wherever villi happen to be in close contact, causing the chorionic cells to be deprived of adequate intervillous circulation. It is, therefore, one of the prominent and generalized features of the early stage of infarction of the "early E" type, provided the nuclei are still round or only slightly

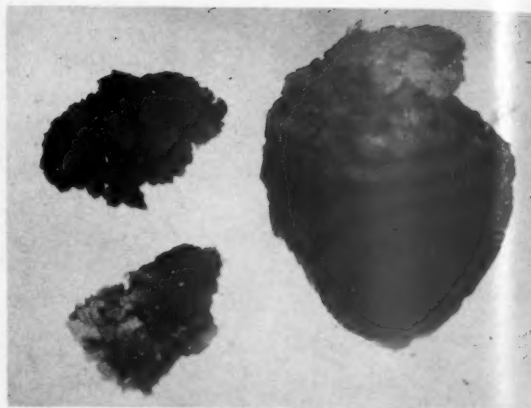


Fig. 8A. Placental fragments from case of erythroblastosis complicated by severe toxemia. Intra-uterine fetal death preceding induction of labor at 6½ months. Placenta extremely large. Light-colored tissue shows large noninfarcted cystic villi, somewhat less crowded than those from the black portions, which show large villi, capillaries of normal size; chorionic tissue layer shows advanced necrosis and structureless karyolytic borders. Crowding of villi and obliteration of intervillous spaces and circulation are due to cystic enlargement and not to distended capillaries.

oval. It is most typically seen in intrapartum toxemia, having developed even in a short span of hours.⁴ Once pyknosis has developed it appears to be permanent, and is present through the succeeding changes which the nuclei undergo.

2. As hypoxia progresses, the next change which the nuclei show is directly due to the marked enlargement of the villi consequent to blockage and distention of the villus capillaries. The pyknotic nuclei, being on the periphery of the villi, are forced to stretch. They become oval, then spindle shaped, and finally break up into a collection of small round fragments. The nuclei, having first suffered hypoxial damage, have now sustained physical damage, karyorrhexis, due to stretch (Fig. 1). This change, following pyknosis, requires an additional span of hours. It may be seen in cases of intrapartum toxemia, if labor has been prolonged or sphincter obstruction complete, but is certain to be present if toxemia began some days before labor.

3. The final nuclear change which indicates toxemia of considerable duration is of the nature of a lysis, causing the fragmented

nuclear material to appear as a marginal smear of pink-blue color—karyolysis (Fig. 8C). Structural breakdown of the villi is seldom seen unless delivery is greatly delayed.

Intervillous fibrination

1. One can readily see the beginning of the outspreading of fibrin deposit along the margin of the villi in the "early E" infarct rapidly extending as thrombosis progresses until, in the "late E" and the "D" infarcts, it has bridged the entire intervillous space. For a short time shadows of red cells may be seen in its meshwork, but soon the appearance is that of a ground glass homogeneous substance (Fig. 2). Evidence of further spread of this process beyond the immediate boundaries of the infarct is often seen. Villi, normal as to size, intervillous space, capillary dimension, and appearance of the nuclear border, appear to be smothered by the intervillous fibrination beyond the area of infarction. It is probable that this process produces increasing placental insufficiency of a truly understandable type and may well account for ultimate fetal death if termination of pregnancy is long delayed (Reference 4, Fig. 7).

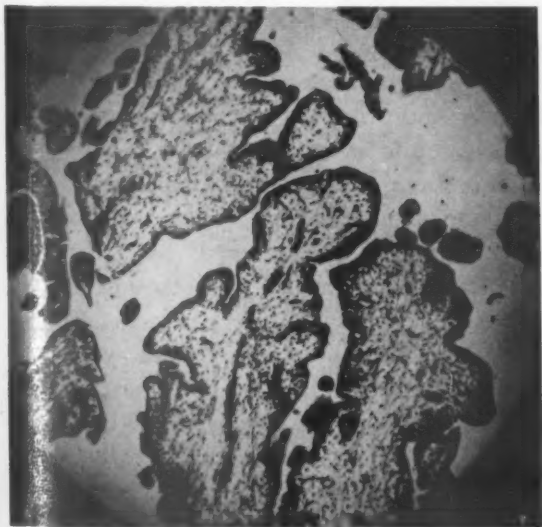


Fig. 8B. Microscopic appearance of villi in light portions. Hyperplasia of chorionic epithelium. Capillaries of normal size. Edematous, cystic change in villus structure. Intervillous space adequate to sustain syncytial layers.

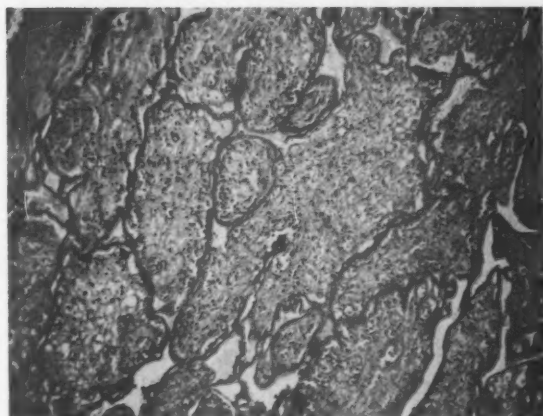


Fig. 8C. Microscopic appearance of dark infarcted portions. Marked diminution of intervillous space resulting in necrosis of chorionic tissue, and karyolysis of nuclei. Capillaries show no distention.

Fibrination is also seen within the distended villus capillaries, apparently originating from overstretched, damaged endothelium of the capillaries, which may not be so immediately harmful to the chorionic epithelium in the maternal intervillous circulation.

Hemorrhage into the substance of the placenta

It is obvious that hemorrhage cannot develop in a sinusoidal circulation, such as the maternal intervillous circulation, since there are so many avenues of dispersion and direction of the flow. Hemorrhagic areas do exist, however, and are recognized as open spaces or excavations designated as "F" lesions; also, clots of varying size and color occur, termed "G" lesions—red, brown, yellow, or white, depending on the age of the clot—or "H" lesions which consist of a semitransparent red to light gray, jellylike substance.² The source of these varieties is probably rupture of one or more villus capillaries, induced by overdistention secondary to temporary placental vein sphincter spasm or, possibly, to temporary compression of a placental vein by a fetal part.

If the fetal blood is compatible with the maternal blood, clotting does not occur. The villi, being temporarily pushed out on all sides, may contain the extravasated blood

for a time, but it soon drains out leaving an empty space. If the bloods are incompatible, thrombosis occurs and the clot passes through the above color changes and striations of fibrin layers finally to become white. It simulates an "A" infarct, but differentiation can be made with the sharp end of a knife blade. Fibrin can be picked out in flakes, but the hyalinized blood of the "A," "B," and "C" infarcts resists dissection and reveals the minute villus projections of an infarct.

Other mechanisms

It is self-evident that diminution or obliteration of intervillous spaces is the important step in the sequence of events which initiates toxemia, and that it must be secondary to placental vein sphincter spasm which is triggered, probably, by oxytocin. The same result may come about by a slower and different pathologic process. It is a well-known fact that severe toxemia of pregnancy may occasionally arise in hydatidiform mole and erythroblastosis (Fig. 8A). In both of these conditions the villi become very large and edematous, and gradually diminish or obliterate the intervillous spaces in some areas.

In addition, in erythroblastosis the syncytial layer becomes much thickened through hyperplasia of the syncytial buds (Fig. 8B). This further encroaches on the intervillous space and increases the source of thromboplastin production and dispersal into the general circulation as hypoxial necrosis of the syncytium increases.

The affected areas become dark or almost black concomitantly with a rapid rise in blood pressure and proteinuria which may terminate in eclampsia, abruptio placentae, or blood coagulation defects if pregnancy is not interrupted. It is now realized that retention of products of pregnancy for several weeks after intrauterine fetal death has occurred may also give rise to increasing danger of intravascular fibrination by eventual release of thromboplastin from subacute necrosis of chorionepithelium and lead to serious coagulation defects.

Should one wish to verify the gross and

microscopic findings which have been described in the foregoing pages and familiarize himself with the types of infarction specific for toxemia, the richest material for showing the "early E" lesion will be found in placentas from any of 3 types of patients: (1) those who have been normotensive and free of proteinuria during pregnancy and on admission to the hospital early in labor, but who show, in catheterized urine at delivery, 2- to 4-plus proteinuria (light cloud to flocculency with heat and 10 per cent acetic acid); (2) those proved by retinal examination early in pregnancy to have vascular disease and who show the characteristic moderate rise in blood pressure with little or no proteinuria in the last 4 to 6 weeks of pregnancy, but at the end of labor show marked hypertension and moderate to flocculent proteinuria; and (3) those who develop fulminating abruptio placentae with no previous signs or symptoms of toxemia.

Examples of "late E" infarction will best be found in cases of recently developed true toxemia. "D" infarction will more likely be found in cases of toxemia of longer duration. Lesions "F," "G," and "H" may be encountered in normal placentas, but are found more often in association with any of the toxic varieties.²

One should not expect to find the pathology of toxemia in placentas from patients who show evidence of hypertensive vascular disease and who are mistakenly considered pre-eclamptic even though they show little or no albuminuria, edema, or headache and no increase in uric acid. They are prone to have sudden superimposed toxemia with rapid development of hypertension, heavy proteinuria, edema, and headache. Under these circumstances the placenta will show extensive "early" and "late E" infarction.

By application of these criteria, the occurrence or absence of toxemia may be diagnosed by examination of the unlabeled formalin-fixed placentas, and placental tissue selected for examination, not at random but on the basis of specific appearance. If the gross findings are questionable, the microscopy findings will furnish the diagnosis.

Comment

The term, "toxemia of pregnancy," owes its continuing acceptability to the fact that the cause and explanation of the symptoms and findings are still considered to be unknown. If, as has been previously stated, the placenta is indispensable to the occurrence of toxemia, the etiological factor must be sought in one or more of its hormones, or in one or more of the breakdown products of infarcted placental tissue.

Too much emphasis has probably been placed upon the part played by generalized arteriolar spasm and the resulting hypertension exhibited by the patient. This is probably not the primary cause; otherwise, we should see the syndrome of toxemia imitated in other clinical conditions in which arterial spasm and hypertension are prominent features. Also, occasional fulminating eclampsia may occur with very mild hypertension and proteinuria and very few retinal arterial spasms.

The hormones produced by the placenta—estrogen, gonadotropin, progesterone, corticosteroids, and presumably oxytocinase—are not, of themselves, known to be toxic and capable of producing the manifestations of the disease. In a recent biochemical investigation,¹¹ supported by a grant from the National Institutes of Health (H-1400), the degradation products of placental autolysis were studied in the hope that some hitherto known or unknown product, possibly guanidine, would be found. The nucleotide pattern was intermediate between that obtained from muscle and that obtained from brain tissue. In the course of artificial autolysis of normal placental tissue, large amounts of uracil, xanthine, and hypoxanthine were obtained. It is probable that these substances are the major antecedents of uric acid which has always shown a significant increase in cases of true toxemia.

Blood taken from the uterine vein during cesarean section of a patient with eclampsia was made available to co-investigator, Dr. Charles Hoover, during these biochemical investigations. Theoretically, this blood should contain, in kind and amount, the

greatest concentration of any significant substance, since it is obtained from nearest the source; it should be less diluted and unaltered by passage through the liver and general circulation. The biochemical results were noninformative, but might well have been significant had blood coagulation defects been the lead pursued at that time.

Blood coagulation defects and the fact that true toxemia is characterized by a specific type of placental injury were investigated during the year 1959.* As has been mentioned, one of the first products of anoxic necrosis of chorionic epithelium is thromboplastin. Although common to necrosis of most tissues, it is especially abundant in placental, decidual, brain, and lung tissue. From its site of production in areas of acute and subacute placental infarction, it initiates intravascular fibrination and thrombosis, first in the intervillous spaces of the infarcted areas and decidual blood spaces with which the infarct is usually in contact; then in the venous return to the right ventricle and to the lungs where capillary blockage and lung injury possibly set up another depot of thromboplastin production and dispersal into the capillary circulation of all important organs and tissues. The visible petechial hemorrhages of the skin and the mucous membranes reflect similar but unseen hemorrhages in the stomach, kidneys, liver, and brain.¹²

Microscopy examination of the kidney in eclampsia, illustrated in the Ross Obstetric Research Conference (1956)¹³ shows partial to complete obstruction of glomerular capillaries, the obstructing substance having a ground-glass appearance similar to and suggestive of the fibrin which is seen in the intervillous spaces of placental infarcts (Fig. 2). The situation could well be likened to that of a Goldblatt kidney with its well-known effects on the blood pressure. Convulsions and coma are logical results of blocked capillaries, hemorrhages, and areas of necrosis in the brain.¹²

*The investigation was aided by continuation of the same grant.

During the past decade much has been written concerning blood coagulation defects in relation to the more serious complications of pregnancy—pre-eclampsia, eclampsia, abruptio placentae, delayed chorionic tissue necrosis incident to prolonged retention of the products of conception after intrauterine fetal death, erythroblastosis (Fig. 8), hydatidiform mole, and, occasionally, septic abortion.

Rapid venous placental sphincter spasm apparently accounts for fulminating eclampsia and abruptio placentae. Slower sphincter spasm is more in keeping with pre-eclampsia, which may extend over a more prolonged but progressive course, terminating in eclampsia or abruptio placentae. In these conditions, syncytial necrosis results from sphincter blockage of placental vein circulation, distention of villus capillaries, enlargement of villi, and deficient intervillous circulation.

In erythroblastosis narrowing of the intervillous space is apparently not the result of placental vein sphincter spasm, but is caused by the edematous enlargement of the villi. In addition, however, the syncytial layer becomes much thicker through hyperplasia of syncytial buds (Fig. 8B), which further narrows or obliterates intervillous space and promotes anoxic necrosis of syncytium. The same mechanism and effects pertain to hydatidiform mole. In septic abortion, infectious necrosis of the decidua apparently causes release of thromboplastin.

In these various obstetric complications, release of thromboplastin is the common denominator, but the mechanism of its source and production has lacked explanation because of disinterest and skepticism concerning placental infarction.

Admittedly, there are gaps in the succession of stages eventuating in blood coagulation defects which need to be filled in through further research, such as identification of the spasmogenic factor which triggers placental vein sphincter spasm (presumably by uninhibited oxytocin), and experimental proof of venous sphincter action in the placenta when a fresh venous segment con-

taining a sphincter is exposed to oxytocin. The development of a method of chemical recognition and assay of blood oxytocin and its inhibitor (oxytocinase?), whereby a critical imbalance might be recognized and possibly control venous sphincter action, appears to be a worthwhile objective.

Dr. Carl J. Wiggers, an eminent physiologist and researcher, has aptly expressed the stages by which an observation and its implications ultimately progress to substantiation: "Observe—Describe—Reflect—Deduce—Verify." The preceding deductions, arrived at from the evidence produced, must await verification by filling in some of the gaps mentioned.

For example, Vara,¹⁴ in a study of 34 normal parturients, found the usual increase in fibrinogen content during parturition, but in 33 patients with toxemia, and also in 19 who had placental detachment, 10 of whom had toxemia in addition, he found a fall in fibrinogen content both during and after delivery, which is what one might expect. Those with premature detachment of the placenta showed extremely low fibrinogen values post partum, particularly when toxemia was an added complication.

Also, Kliman and McKay¹⁵ showed that intravenous injection of bacterial endotoxin into rabbits induces an intravascular formation of fibrin thrombi which may be found in the capillaries of the lungs, liver, spleen, and kidney. (the generalized Shwartzman reaction). Bilateral cortical necrosis takes place in the kidneys following a second injection. While these findings are developing there occurs a marked drop in the circulating fibrinogen. This reaction is completely averted by the administration of heparin preceding injection of the toxin. According to these authors, heparin prevents the action of thrombin on fibrinogen and also acts as an antithromboplastic agent by diminishing prothrombin complex in the circulating blood.

Condie, Hong, and Good¹⁶ showed that activation of the fibrinolytic process by streptokinase was also able to prevent the generalized Shwartzman reaction. Kliman

and McKay's¹⁵ work confirmed this and, in addition, showed that while fibrinolytic activity prevents deposition of thrombi, it was not able to destroy preformed thrombi after a 24 hour period, especially those which were microscopic. Their observations suggested that the fibrinolytic enzyme must be occluded or embedded within the microscopic thrombi in order to destroy them and restore circulation.

The fact that acute infarction of the placenta accompanied by heavy proteinuria often develops intra partum and is accompanied by a significant drop in fibrinogen content in the blood in the intra- and immediate postpartum periods¹⁴ lends credence to the impression that oxytocin, which apparently initiates labor, may also initiate intrapartum toxemia in at least 10 per cent of patients through action on the placental vein sphincters.

The relevance of the findings obtained in the above experiments to the concept that toxemia of pregnancy is, in all probability, a manifestation of intravascular fibrination induced by placental thromboplastin is indeed more than a mere coincidence.

Suffice it to say that the foregoing pieces of the oft-mentioned jigsaw puzzle of toxemia of pregnancy seem to furnish a pattern upon which the necessary and missing pieces of evidence may be supplied by design, rather than haphazardly, and may lead to the solution of what has been a most baffling problem.

Considering the fact that intravascular fibrination is a physical rather than a toxic phenomenon in its effects, it is likely that some comprehensive term other than toxemia of pregnancy will be found preferable, possibly intravascular fibrination of pregnancy, under which all of the aforementioned conditions arising from critical narrowing of the intervillous spaces may be grouped.

Conclusions

The criteria by which extensive or localized placental infarction may be recognized in cut strips of formalin-fixed placentas may be listed as follows:

Gross examination.

1. Color changes from dark, to black, to brown, delineating the infarcted areas from the adjoining normal placental tissue of light gray color.
2. Increased firmness of the infarcted areas in the same order as color.
3. Increased resistance to bending of the strip through the infarcted area, in accordance with color changes.
4. Increased resistance to expression of fixation fluid from the infarcted area, due to increasing exclusion of the fluid by the increasing intervillous thrombosis, in the same order.
5. Increased reflection of light from the moistened and rubbed infarcted surface, likewise in the same order.
6. Greater thickness of the placenta in the infarcted area(s).

Microscopy examination.

1. Universal enlargement and crowding of the individual villi in the infarcted area with resultant partial or complete thrombosis and cessation of intervillous circulation.
2. Intensification of nuclear staining, stretching, elongation, and finally fragmentation and lysis of the chorionic nuclear material in the infarcted area according to duration of infarction.
3. Marked enlargement, distention, congestion, and thrombosis of villus capillaries.

Increasing familiarity with these criteria will bring about more uniformity in statistics relating to the frequency of pre-eclampsia and abruptio placentae, and avoid labeling hypertensive vascular disease as a form of toxemia and mistaking rupture of the marginal sinus for marginal abruptio placentae.

In our opinion, acute and subacute placental infarction with release of thromboplastin is the cornerstone to an understanding of the so-called toxemia of pregnancy.

We wish to thank Dr. W. J. Spanos, a member of the late Dr. LeRoy Calkins' staff, Department of Obstetrics and Gynecology, University of Kansas Medical School, for furnishing us with a specimen of blood, drawn at the time of cesarean section, from the uterine vein of a patient with eclampsia.

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The electronic evaluation of the fetal heart rate

V. The vagal factor in fetal bradycardia

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THE present clinical criteria of fetal distress are based largely on changes in the fetal heart rate and the passage of meconium. There is no general agreement as to the significance of fetal bradycardia or tachycardia, separately or together, or the presence of meconium alone or with either.¹⁻¹⁵

One of the major difficulties is related to the inherent inaccuracies of periodic auscultatory sampling of the fetal heart rate.^{14, 16} Further, there is need for meticulous long-term pediatric follow-up to determine sublethal fetal damage.

With electronic techniques previously developed for continuous monitoring of the fetal heart rate during labor and delivery,^{16, 17} over 100 cases of fetal distress (so classified by the obstetrician on the basis of his individual criteria) have been monitored during the past 3½ years. This has provided an opportunity to observe the various types

of fetal heart rate patterns associated with clinically diagnosed fetal distress and to compare them with one another and the ultimate development of the infant.

During this study certain patterns of bradycardia were associated consistently with specific conditions such as increased intracranial pressure, abnormal uterine activity, maternal hypotension, and probable umbilical cord compression. In clinically diagnosed fetal distress, the type of bradycardia probably associated with umbilical cord compression^{16, 18-20} occurred most frequently. The majority of these infants did not appear depressed at birth in spite of profound fetal bradycardia and the passage of fresh meconium. In an earlier report¹⁸ it was suggested that this type of bradycardia might be due largely to vagal cardiovascular reflex activity rather than to primary oxygen lack.

This report describes fetal electrocardiographic changes with "cord compression" bradycardia and the alterations in fetal heart rate pattern following the administration of a vagal blocking agent (atropine) to the mother.

Patients and procedures

Four of the fetal heart rate patterns discussed in this study have been selected from 105 cases of fetal distress, where the obstetrician requested aid with a *clinical* problem. The other was recorded from a "normal" labor. They have been recorded with techniques previously described (scalp elec-

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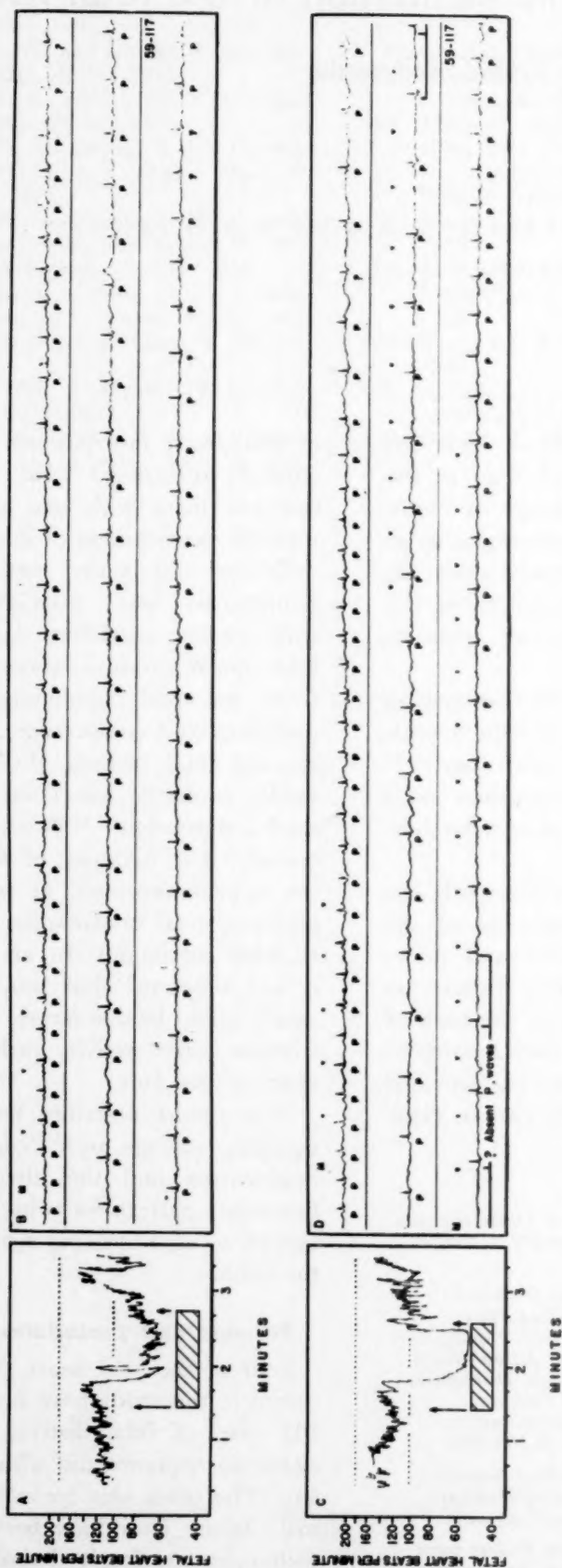


Fig. 1. *A*, The pattern of fetal bradycardia associated with a uterine contraction recorded from a fetus who had the cord loosely wound around his neck at delivery. *B*, The sinus mechanism of the bradycardia is evident from the presence of P waves (marked by P) before each QRS complex. Low amplitude baseline elevations due to the maternal ECG are occasionally seen, these are marked *M*. *C*, Same patient as in Fig. 1, *A* and *B*. Record made 5 minutes earlier. *D*, There appears to be a shift in pacemaker with P waves absent for some QRS complexes and questionably absent in others.

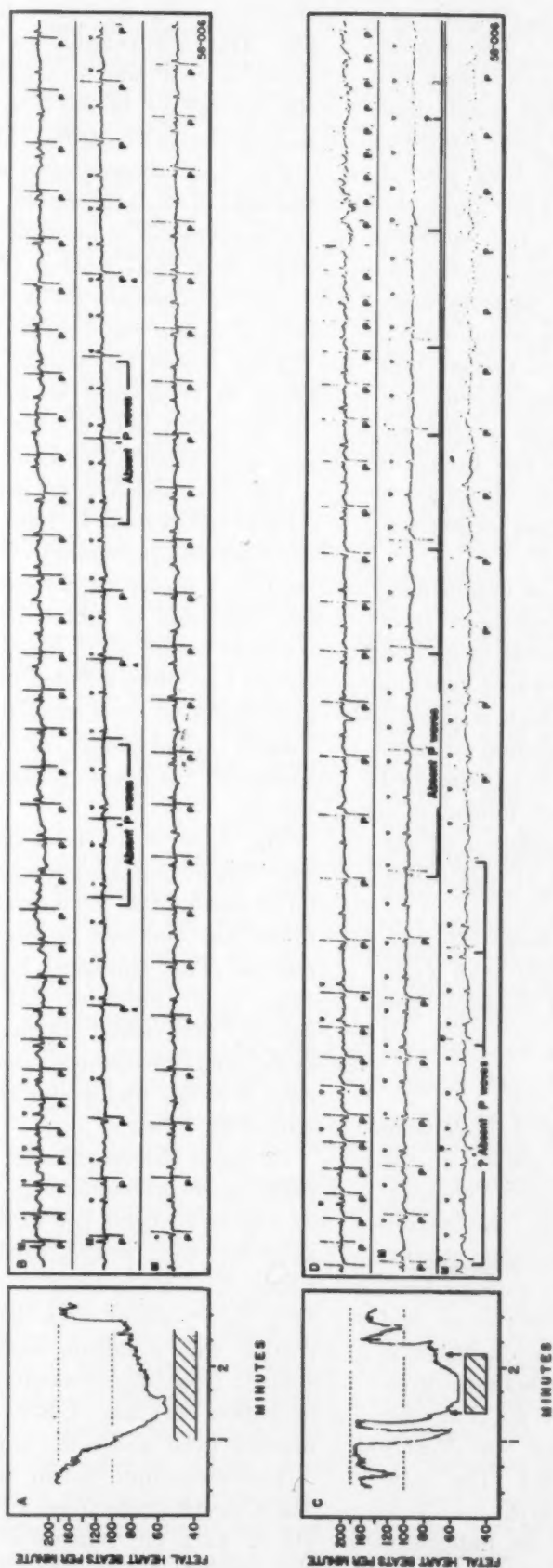


Fig. 2. *A*, Fetal heart rate pattern recorded from a fetus with prolapse of the umbilical cord. The profound bradycardia was as low as 33 beats per minute. (Cardiotachometer does not plot below 50 beats per minute.) *B*, Note sinus arrest and nodal rhythm. Note shortened P-R interval associated with three P waves just preceding and following sinus arrest. Low amplitude maternal ECG are marked by *M*...., fetal P waves by *P*. *C*, Same patient as in Fig. 2. *A* and *B*. Profound bradycardia and sinus arrest again present. *D*, Note nodal rhythm with shifting focus where there are changes in the QRS complex (marked by *o* above complex in lower tracing).

trode, 59-117, 59-157, 60-001, 60-006), intrauterine electrode (58-006). The graphs were constructed from the continuous recording of the fetal ECG made during that portion of the patient's labor after fetal distress was suspected and have been plotted on a semilogarithmic scale. They show the instantaneous rather than the average rate^{16, 18-20} and illustrate what are considered typical fetal heart rate patterns associated with umbilical cord compression. While it may be reasonable to suspect that a fetal heart rate pattern is due to umbilical cord compression, this cannot be proved. However, similar patterns have been recorded consistently following compression of the umbilical cord at cesarean section and in cases of prolapsed cord.^{16, 19}

Since this study was done in urgent clinical situations, uterine contractions have been determined by abdominal palpation and correlated with the increased baseline activity of the fetal ECG which is present during contractions. The duration of each contraction is indicated by a crosshatched oblong and associated arrows immediately beneath the tracing. The condition of the newborn infant was assessed by the Apgar score.²¹

The various types of fetal heart rate patterns associated with umbilical cord compression have been described in detail previously.^{16, 18-20}

Results

The tracings shown in Fig. 1, *A-D* were recorded from a 21-year-old patient in the forty-third week of gestation with the cervix at 4 cm. of dilatation and the vertex at station 0. The patient was being studied for evaluation of fetal heart rate patterns in normal labor. Although bradycardia had not been detected clinically, continuous monitoring revealed a fetal heart rate dropping with contractions below 80 beats per minute. At delivery the cord was loosely wound around the baby's neck. The baby was in good condition (Apgar 8).

The record of Fig. 1, *A* is the pattern of bradycardia noted during a contraction. At

its lowest point the rate is 60 beats per minute. This bradycardia had a sinus mechanism since P waves can be seen readily in the photograph of the fetal ECG's recorded during the bradycardia (Fig. 1, *B*).

Fig. 1, *C* demonstrates a similar pattern recorded 5 minutes earlier. In this instance the bradycardia is more profound. The corresponding ECG tracing (Fig. 1, *D*) shows a sinus mechanism for a time: sinus arrest occurs during the bradycardia, then nodal rhythm ensues for a short time. There appears to be a shift in pacemaker with P waves absent before some QRS complexes and questionably absent in others.

Fig. 2, *A* and *B* shows similar records of a 22-year-old gravida iv, para iii, white woman at 25 weeks of gestation where the umbilical cord had prolapsed through the cervix before the onset of labor. This case has been reported previously.¹⁹ Short segments of the record have been selected to demonstrate the mechanism of fetal bradycardia in the immature infant under circumstances where umbilical cord compression was probably present.

Fig. 2, *A* is the fetal heart rate pattern recorded during a contraction shortly before fetal death. The fetal bradycardia is profound and becomes as low as 33 beats per minute. The associated fetal ECG tracing (Fig. 2, *B*) indicates that sinus arrest occurred, that nodal rhythm ensued for 2 beats, sinus mechanism was present for the next 2 beats, and nodal rhythm again occurred for 3 beats.

As labor continued the bradycardia became more profound (Fig. 2, *C*). This was as low as 31 beats per minute and was too slow for the present cardiometer to count. The concomitant fetal ECG tracing (Fig. 2, *D*) shows sinus arrest and a nodal rhythm with a shifting nodal focus. This is evident from the momentarily altered configuration of the QRS (lower tracing, marked by *o* above the complex).

The recordings shown in Fig. 3, *A*, *B*, and *C* were made from a 27-year-old gravida x, para vii, patient at term who had had one abortion and on whom studies were

made because of clinically detected fetal bradycardia. At delivery the cord was snugly wound around the baby's neck and shoulder. The baby at birth was in good condition (Apgar 7).

Fig. 3, *A* was recorded at 3 to 4 cm. dilatation with the vertex at station minus-1. The mother was given atropine intravenously at the beginning of the tracing. Between 10 and 15 minutes after the administration of atropine the average fetal heart rate became higher and less irregular. The effect of atropine on the fetal heart rate is emphasized further by comparison of Fig. 3, *B(i)*, which was recorded just before atropine was given, and Fig. 3, *B(ii)*, which was recorded 19 minutes after its administration.

Alterations in the mechanical relationship of the fetus and the umbilical cord have been thought to be associated with variations in the fetal heart rate.²⁰ In this patient the umbilical cord was snugly wound around the neck and shoulder of the infant. Pressure applied to the fetus through the abdominal wall of the mother had a different effect on the fetal heart rate pattern before (Fig. 3, *C(i)*) and after (Fig. 3, *C(ii)*) atropine. The effect of vomiting on the fetal heart rate pattern was also modified by atropine (Fig. 3, *C(iii)* and 3, *C(iv)*).

The fetal heart rate pattern in Fig. 4 was made from a 20-year-old primigravida with the cervix at 9 cm. dilatation and with the vertex at station plus-1. About one hour earlier the fetus was found clinically to have bradycardia as low as 60 beats per minute immediately following contractions but no meconium was noted. Atropine was administered 5 minutes after the beginning of the tracing. Six minutes later there was a definite change in the patterns of bradycardia and an elevation in rate to 170 beats per minute. Because of the clinical diagnosis of fetal distress, the obstetrician felt that immediate delivery should be effected. This was achieved by difficult midplane forceps rotation and extraction. The umbilical cord was loosely wound around the baby's neck. Immediately after birth the baby was depressed,

but scored Apgar 10 after 5 minutes. The initial depression was probably associated with the forceps delivery.

Fig. 5, *A*, *B*, and *C* are the fetal heart rate patterns recorded from a 22-year-old, gravida ii, para 1, in whom the clinical diagnosis of fetal distress was made on the basis of a fetal heart rate of 120 beats per minute, irregularity and beat-to-beat arrhythmia. At delivery the umbilical cord was tightly wound around the baby's neck. About 20 c.c. of fresh, unmixed meconium was present at the external cervical os. The baby was in good condition (Apgar 8). Fig. 5, *A(i)* was recorded just prior to the administration of atropine. The fetal heart rate varied from 120 to 150 beats per minute, and there were numerous premature nodal contractions and moderate irregularity. The second section, Fig. 5, *A(ii)*, which begins 10 minutes after the atropine was given, shows minor changes. Thirty minutes after the administration of atropine (Fig. 5, *B*) there has been a striking change in the record. There is slight irregularity, there are no premature nodal contractions, and the baseline rate is a little higher than before atropine administration. The first section of Fig. 5, *C(i)* (79 minutes after atropine) shows a further acceleration of the baseline fetal heart rate to 150 to 170 beats per minute and a few premature nodal contractions. As the atropine effect decreased, Fig. 5, *C(ii)*, (139 minutes after administration) the baseline rate returned to 130 beats per minute, mild irregularity was again noted, and numerous premature nodal contractions were seen.

Comment

The fetal heart rate patterns presented in this study were from 4 patients in whom the diagnoses of fetal distress were made clinically and one case of clinically undetected fetal bradycardia. In each of the 5 some type of umbilical cord complication probably was present. In our study, to date, of the fetal heart rate in clinically diagnosed fetal distress, a "cord compression" bradycardia pattern has been predominant.^{18, 18-20}

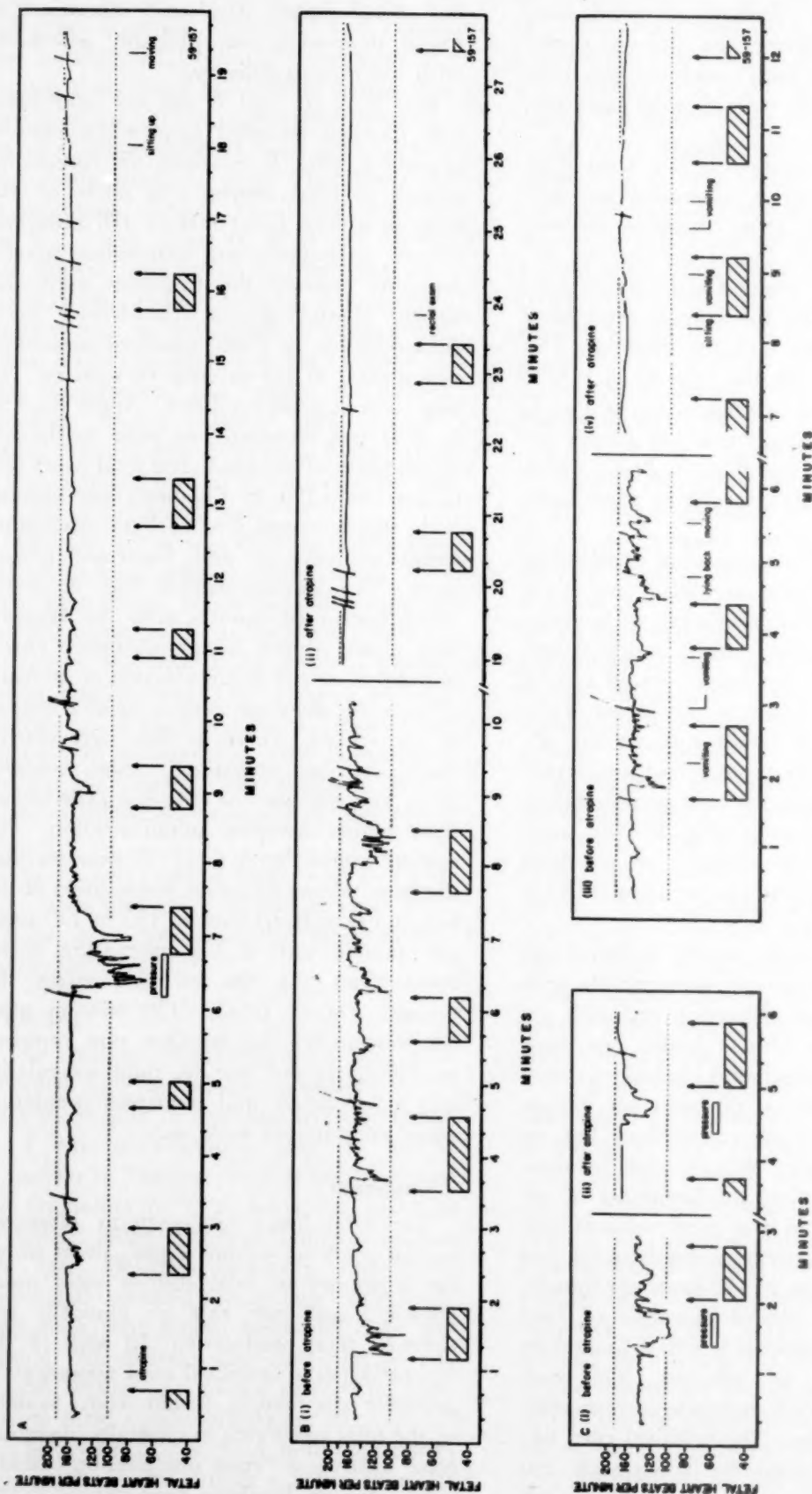


Fig. 3. A, Alteration seen in the fetal heart rate pattern between 10 and 15 minutes after the administration of atropine to the mother at the beginning of the tracing (infant had the umbilical cord snugly wound around neck and shoulder at delivery). Note the smooth and elevated baseline rate in the latter part of the record. B(i), Fetal heart rate pattern just before the atropine was given. B(ii), General acceleration in baseline level, absence of irregularity 19 to 29 minutes after administration of atropine. This record contrasts sharply with that of Fig. 3, B(i). C(i) and C(ii), Modification of fetal heart rate pattern associated with pressure on the lower abdomen of the mother after atropine administration (Fig. 3, C[i] before, Fig. 3, C[ii] after). C(iii) and C(iv), Modification of the effects of vomiting on the fetal heart rate pattern after atropine administration (Fig. 3, C[iii] before, Fig. 3, C[iv] after).

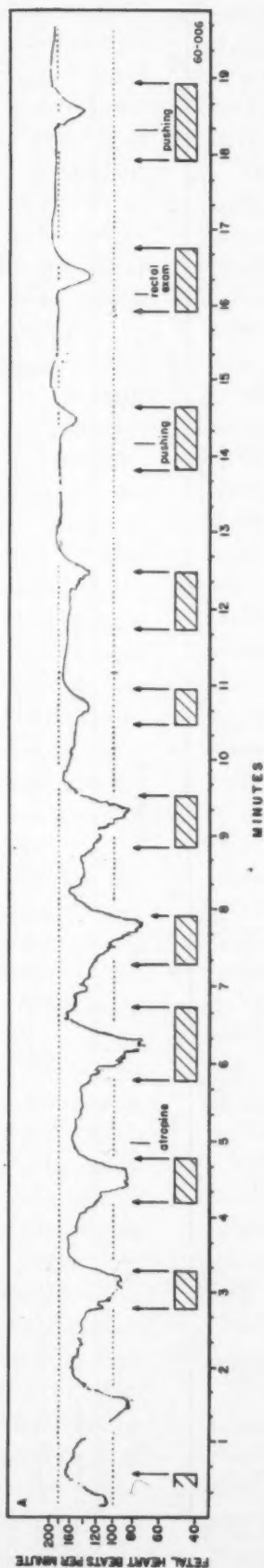


Fig. 4. Fetal heart rate pattern recorded at 9 cm. dilatation with the vertex at station plus-1. At delivery the umbilical cord was loosely wound around the baby's neck. Atropine was given to the mother as indicated in the figure. Note the acceleration of rate and modification of the bradycardia associated with contractions after atropine administration.

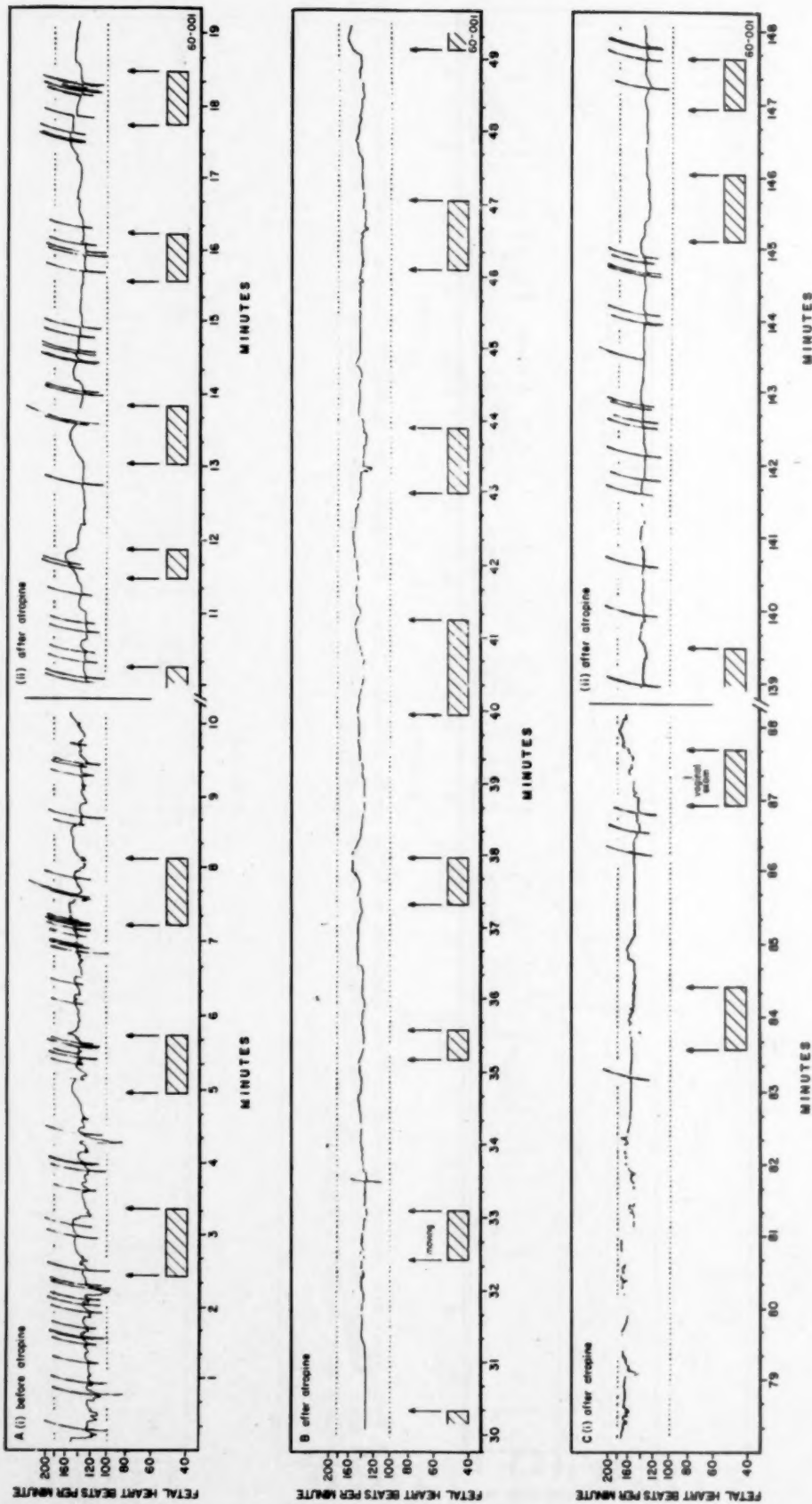


Fig. 5. A, B, and C, Fetal heart rate patterns recorded of a fetus who had the umbilical cord tightly wound around his neck. About 20 c.c. of fresh meconium was noted at delivery. A(i), Fetal heart rate varying from 120 to 150 beats per minute, numerous premature nodal contractions, and moderate irregularity before the administration of atropine. A(ii), Minor changes 10 minutes after atropine. B, Thirty minutes after atropine. Baseline rate 130 to 140 beats per minute, no premature nodal contractions, less irregularity (compare with Fig. 5, A). C(i), Seventy-nine minutes after atropine. Baseline rate 150 to 170 beats per minute, few premature nodal contractions. C(ii), One hundred and thirty-nine minutes after atropine. Baseline rate 130 beats per minute and many premature nodal contractions.

Bradycardia. Fetal bradycardia, cardiac irregularity, and the passage of meconium are the chief criteria for the clinical diagnosis of fetal distress. In order to determine the clinical significance of these signs, it is necessary to understand their underlying physiologic mechanisms. Fig. 1, *A-D* and 2, *A-D* clearly indicate that much of the bradycardia (probably associated with umbilical cord compression) is due to a sinus mechanism which when arrested is replaced by a nodal rhythm. Strong stimulation of the vagus nerves in the human²² and in animals²³⁻²⁵ will produce vagal heart block with nodal or ventricular escape. It is probable, therefore, that much of the bradycardia associated with compression of the umbilical cord of the human fetus, like that of fetal animals,²⁶⁻²⁹ is due to vagal stimulation.

In the human adult, cardiac arrhythmias are also associated with increased vagal tone.³⁰⁻³¹ This seems to be true also of the fetus since the administration of atropine to the mother was associated with an acceleration in the baseline fetal heart rate and absence of premature nodal contractions (Fig. 5, *A-C*).

The suggestion that vagotonia is an important factor in fetal bradycardia associated with umbilical cord compression is supported further by the modification of the fetal heart rate pattern after the administration of atropine. In general, there is an acceleration in baseline rate, with less irregularity and less bradycardia with uterine contractions (Figs. 3, *A-C*, 4, and 5, *A-C*). These findings are consistent with the modifications of fetal heart rate patterns in animals whose umbilical cords were compressed following atropine injection or vagotomy.²⁶⁻²⁹

The vagal factor in bradycardia. The consistent relief of fetal bradycardia reasonably suspected to be due to umbilical cord compression by vagal blocking with atropine suggests that much of the fetal bradycardia noted with cord compression is of reflex nature. This bradycardia, therefore, probably represents an attempt of the fetus to adjust to altered fetal hemodynamics. In this sense it is, therefore, an adaptive or

compensatory mechanism and within limits is not sinister. If, however, cord compression is severe and prolonged, it must inevitably lead to anoxemia and generalized fetal hypoxia.

Meconium. While it is well known that with vertex presentations there is an increased incidence of perinatal mortality and morbidity when meconium is passed during labor,^{2, 3, 9, 12, 32} there is no general agreement as to the mechanism of production. The majority of workers feel that this is related to hypoxic stimulation of the large bowel and external sphincter. However, there are many instances of fetal death where meconium is not found, and quite frequently fresh meconium is passed and the baby is obviously not hypoxic. The infant whose fetal tracing is illustrated in Fig. 5, *A-C* is a good example. Here there is evidence of vagotonia (many premature nodal contractions which were absent following maternal atropine injection, acceleration in baseline fetal heart rate, with a return to the former pattern after the effects of atropine had worn off) and the presence of fresh, unmixed meconium (suggesting recent passage) without any suggestion of fetal depression.

It is interesting to note that vagal stimulation produces hyperperistalsis of the large bowel and relaxation of the external anal sphincter.^{22, 33} There is a possibility, therefore, that a percentage of fetuses who pass meconium are reflecting merely vagotonia and not hypoxia.

Clinical implications. The role of the vagus in clinical fetal distress is yet unknown. This study suggests that some of the fetal bradycardia associated with clinically diagnosed fetal distress may be compensatory and not necessarily evil in the sense that it reflects a compromised fetal environment.

It is urged that fetal bradycardia not be treated with atropine since its therapeutic role, if any, in this situation must await extensive study. Until there is a clearer understanding of clinical fetal distress, it would be wise to continue with our present methods of therapy.

Summary

1. Much of the fetal bradycardia associated with umbilical cord compression is probably due to vagotonia.

2. The administration of atropine to the mother altered markedly the fetal heart rate patterns of 3 fetuses who at delivery had probable umbilical cord compression. (These cases were selected from a series of 31 patients who had similar responses.)

3. Fetal bradycardia may be, within limits, a compensatory or adaptive mecha-

nism and, therefore, does not indicate necessarily fetal hypoxia but may reflect increased vagal tone.

4. The passage of meconium may be due not only to hypoxic stimulation of the large bowel and relaxation of the anal sphincter but may be caused by increased vagal tone.

5. The usual happy outcome of clinically diagnosed fetal distress supports the idea that fetal bradycardia and the passage of meconium do not always indicate a compromised fetus.

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Observations on the fetal heart rate

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THE fetal heart rate has been of great interest to obstetricians for many years. In recent years techniques of electrocardiography¹⁻⁸ have permitted accurate recording of instantaneous fetal heart rates. However, most studies of fetal heart rate have been done in abnormal situations. It was thought to be desirable that observations of fetal heart rate should be made at various stages of gestation prior to labor, in normal resting patients. The effects of variations of maternal respiratory gases were also studied.

Materials and methods

Thirty-six Negro patients who had no clinical abnormalities were selected at various stages of gestation from the Tulane Obstetrical Service of Charity Hospital at New Orleans. The technique and instrumentation used for fetal electrocardiography have been described previously.⁷ The patients were placed in a comfortable recumbent position

and an initial tracing was taken to ascertain that the fetal complexes were clearly discernible. All patients were allowed to rest for 10 to 15 minutes with the electrodes in place. After this the observations were made. For one group of patients, nothing was done except to record the fetal electrocardiogram for 10 to 15 minutes. A second group was used to study the effects on the fetal heart rate of variations of maternal respiratory gases. With part of this group the fetal electrocardiogram was recorded while the mother breathed air for 2 minutes, then medical oxygen for 10 minutes, and finally air for 2 minutes. The remainder of this group breathed air for 1 minute, then air with 5 per cent carbon dioxide for 2 minutes, and then air for 1 minute. For the respiratory gas variations a pinch clamp was placed upon the mother's nose and she was allowed to breathe through a rubber mouthpiece. This mouthpiece was connected to a valve which could be adjusted to admit only room air or only the gas in a reservoir.

Calculations. The instantaneous fetal heart rate was determined by measuring the distance between consecutive fetal complexes on the tracing, converting this into lapsed time, and calculating the minute rate. Minute rate was used to express instantaneous heart rate since this is a universally used method. The one second interval timer on the Sanborn recorder was used constantly to avoid any error due to possible variations in paper speed. The instantaneous minute rate for each cardiac cycle was plotted on linear graph paper.

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Taken in part from a thesis submitted by Drs. Campbell and Williams to the School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine.

**Part of this work was done during tenure of a Fellowship of the American Heart Association.*

***Part of this work was done during tenure of a student Fellowship of the Louisiana Heart Association.*

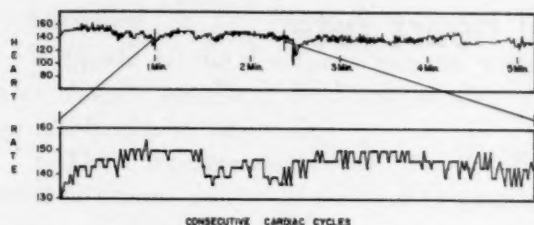


Fig. 1. Part of this graph of the instantaneous fetal heart rate has been expanded to show the details of the frequently occurring small changes.

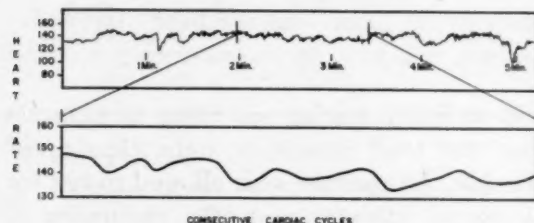


Fig. 2. Part of this graph of the instantaneous fetal heart rate has been expanded to show a less frequently occurring greater amplitude change. The more rapidly occurring changes have been eliminated from the lower part of the illustration.

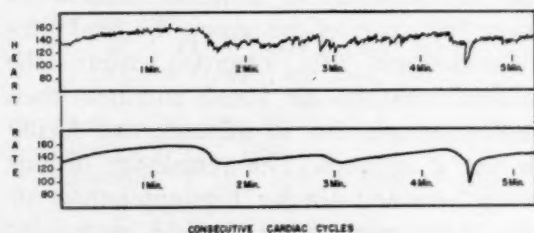


Fig. 3. A graph of the instantaneous fetal heart rate. The rate changes illustrated in Figs. 1 and 2 have been omitted from the lower part of the illustration to show the more slowly occurring changes.

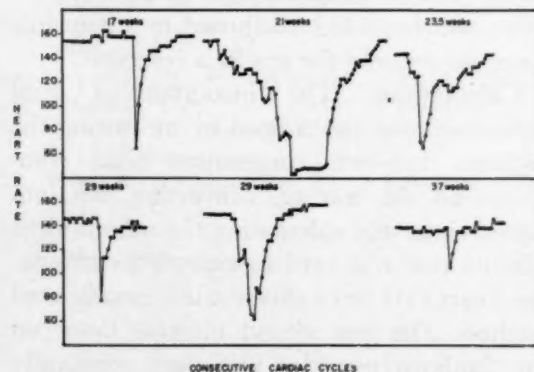


Fig. 4. Some of the precipitous drops in the fetal heart rate are shown. The example occurring at 21 weeks' gestational age is unusual, and the precipitous drops observed resembled the other five examples.

Results

The fetal heart rate may be characterized as inconstant, with periods of constant rate being the exception rather than the rule. Four types of rate change were seen. The first type consisted of small rate changes occurring rapidly and irregularly (Fig. 1). With this type of change the minute rate increased or decreased 5 or 10 from one cardiac cycle to the next, and as many as 14 to 35 of these changes occurred per minute. This type of rate change was seen in all tracings at all gestational ages. Occasionally, the fetal heart rate was constant for a few cycles, but rarely was there a steady rate of increase or decrease.

The second type of rate change was of a greater degree, with the change in minute rate being about 20 or 30 (Fig. 2). These rate changes occurred about three to five times per minute. This type of change was seen at all gestational ages and was present in 66 per cent of all tracings.

The third type of rate change tended to be of greater amplitude, with a change in minute rate of 20 to 40 (Fig. 3). With this change the rate would slowly increase over a period of 3 to 4 minutes and would decrease in about 15 to 20 seconds. This type of rate change occurred one or more times in 75 per cent of the cases.

The fourth type of rate change was a precipitous drop in minute rate of 30 to 100 (Fig. 4). The decrease in rate usually occurred during 2 to 4 cardiac cycles. The rate would begin to increase to normal rates after 1 to 3 beats, but the increase in rate was not as rapid as the decrease, taking 5 to 15 cardiac cycles before the usual rates were resumed. In one case the fetal heart rate stayed below 55 beats per minute for 15 cardiac cycles. These marked precipitous rate changes were seen after the sixteenth week at all gestational ages studied, and occurred in 47 per cent of the cases studied. They occurred less frequently and the decrease was not as marked after the twenty-ninth week. There were equal numbers of male and female babies exhibiting this phenomenon. All of the rate changes were gen-

erally more frequent and of a greater degree between the twenty-second and the twenty-ninth week of gestational age.

During the time of the oxygen administration, no changes from previous rate patterns were detected at any stage of gestation. With the administration of 5 per cent carbon dioxide, the maternal heart rate increased as expected; however, the fetal heart rate did not change from its control pattern. No detectable uterine contractions occurred in any of the patients while these observations were being made.

Comment

Some of the plotted variations of the first type of rate change are due to error in measurement, since increments will be multiples of the smallest unit of measurement which can be visually determined. However, when the paper speed is increased to 100 mm. per second to decrease these measurement errors, the heart rate is still quite irregular and the increments in rate change, although smaller, are less uniform.

The occurrence of pronounced slowing of rate, both periodically and at random, in normal pregnancy after the sixteenth week of gestation was an unexpected finding. This observed rate change is a true rate change and is not due to maternal complexes obscuring some of the fetal complexes. Coinci-

dence of complexes would result in an acute apparent rate change, both slowing and accelerating, and would alter the shape of the maternal complexes. At present this rapid slowing and slower recovery of the fetal heart rate must be called a normal variation. The importance of this phenomenon lies in differentiating it from rate slowing due to obstetric pathology.

The small increase in arterial oxygen tension when normal patients breathe oxygen may explain the lack of fetal heart rate change in this group. The lack of fetal heart rate change with a carbon dioxide increase of this magnitude may be due to carbon dioxide levels above the threshold of response, the small pulmonary blood flow, or the absence of respiratory muscular activity.

Interpreting any physiologic or pharmacologic rate change phenomena of the fetal heart is difficult and the lesser degrees of change are masked by the irregularity of the fetal heart rate.

Summary

Observations of the fetal heart rate at various stages of gestation in normal patients are presented. The fetal heart rate is noted to vary almost constantly, and four types of heart rate change are described. The administration of oxygen or 5 per cent carbon dioxide in air to the mothers does not change the fetal heart rate pattern.

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Determination of fetal weight in utero

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FOR years practicing physicians have been concerned with the inability to determine accurately fetal weight in utero. Tragedy still occurs as a direct result of inadequate knowledge regarding intrauterine fetal weight. A re-evaluation of this problem was undertaken in the hope of evolving a more precise method.

A more accurate estimate of fetal weight could contribute to better care in dealing with prematurity, postmaturity, fetopelvic disproportion, erythroblastosis fetalis, third trimester bleeding, maternal diabetes, chronic nephritis, toxemia of pregnancy and other situations benefited by knowledge of intrauterine fetal size and weight.

To be of practical significance, our original objective required that such estimate must be accurate within one-half pound of actual birth weight in at least 85 per cent of the cases studied.

Review of literature

In 1935, Ball and Marchbanks² introduced an instrument, the pelvicephalometer, which permitted measurement of the mean circumference of the fetal head from both the anteroposterior and lateral films, irrespective of the obliquity of the fetal skull position. After studying 60 cases, these authors believed this method to be reliable within one-half pound in over 85 per cent of their cases.

In 1940, Guerriero, Arnell, and Irwin,⁷ using Ball's method, concluded that for vertex presentations at term, the estimates

were reasonably accurate, but a statistical analysis was not reported.

In 1943, Ball and Golden¹ varied this technique to include anteroposterior and lateral films taken with the patient in the erect position. By so doing, the relation of the uterus to the axis of the maternal body remained unchanged and the effect of gravity on the uterus and its contents was the same in both projections.

In 1937, Hodges⁸ presented a method of pelvimetry using stereoscopic views. On the basis of Scammon-Calkins anthropometric studies, he worked out a method for determining intrauterine fetal age. Hodges introduced an obstetrical jacket of Bakelite material to maintain fetal position when manipulating patients for various film views. He also introduced a graphic method to determine the object-film distance from 90 degree triangulation films in an attempt to correct for distortion. This proved to be quite accurate in determining fetal age, and the author concluded that a rather large biologic variation existed between fetal age and fetal size.

In 1938, Hodges and Hamilton⁹ emphasized that the diameters to be measured must lie parallel to the plane of the film or foreshortening would result and incorrect prediction of age and size was favored. They indicated that the circumference of the fetal skull was a valuable guide to fetal age. Hodges and Nichols¹⁰ also introduced a new x-ray table enabling the patient to remain in one position—supine—while the anteroposterior and lateral films were taken. This, of course, minimized the fetal and maternal

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motion and was the roentgenographic technique used in this study. The 90 degree apparatus (the term applied by Hodges) is a motor-driven reciprocating Potter grid with an x-ray tube attached to a cradle mounted in such a manner that the cradle may be rotated 90 degrees with the table remaining stationary.

In 1940, Snow and Lewis¹⁸ outlined a simple technique for determining fetal age using anteroposterior and lateral films, fetal skull circumference, a correction factor for object-film distance and a slide rule designed by the senior author to ascertain the final reading. They stated: "We feel that accurate and simple roentgen pelvimetry is a forward move toward reducing the number of cases which will be subjected to an unsuccessful or undesirable trial of labor. For it is our suspicion that mental disease statistics may someday show that every labor which concludes with a living baby is not necessarily, from all aspects, a successful one."

In 1943, Cave³ described a method of cephalometry using the object-film and tube-film distance in a formula to determine true diameters of the fetal head. Correlation with fetal weight was to be considered at a later date.

In 1946, Weinberg, Rockaway, and Scadron¹⁹ found that the corrected circumference of the head by roentgenography was accurate within 1 cm. when checked with the head circumference at birth. Employing the Ball pelvicephalometers for determination of the fetal weight in utero, they found that over 25 per cent of the cases differed more than one pound. They believed that this was due to the difference in over-all fetal length and the muscular and fatty development of the infant, not to faulty roentgenography.

In 1951, McElin and associates¹⁵ employed Cave's method of roentgen cephalometry in 22 cases taken at random. They noted that measurement of the diameters of the fetal skull in utero were accurate in 85 to 90 per cent of the cases. No mention was made of its accuracy in determining fetal weight. Although their experience with this method

did not indicate precision, they felt it was deserving of further investigation.

Donaldson and Cheney,⁵ in 1948, applied the Ball method of pelvicephalometry in 338 cases and concluded that the birth weight of an infant could be predicted within 8 ounces in 36 per cent and within 16 ounces in 62 per cent of the cases studied. In the same year, Colcher and Sussman⁴ made direct measurements by placing a centimeter ruler at midsacrum prior to roentgen examination. They were impressed by the importance of the suboccipitobregmatic and biparietal diameters as indicators of fetal size, but no statistics were presented. After summarizing a study of 1,000 cases using clinical and roentgenographic methods, Dyer, in 1950,⁶ concluded that no method for estimation of fetal size is totally reliable.

In 1953, Jacobs^{11, 12} presented a review based on a study of pelvic roentgenograms taken with the patient in a standing position in 761 cases. He was impressed with the fact that in most instances the biparietal diameter applied itself or engaged in the true conjugate diameter of the pelvis. In correlating the biparietal diameter with the fetal weight he found that two thirds of the cases fell along the "trend of weight at birth" line and did not exceed 0.9 pound above or below the trend value for a given biparietal diameter.

Other investigators^{14, 16} have used purely clinical methods to estimate the fetal weight in utero by examining the patient's abdomen and its contents. In 1953, Poulos and Langstadt¹⁷ published their work on 21 cases correlating the volume of the uterus during labor with fetal weight. Recognizing the inaccuracy of x-ray estimations of fetal weight, they developed a volumetric technique based on transverse and longitudinal measurements of uterine enlargement with the obstetrical calipers in a manner outlined diagrammatically by the authors. They reported that 68 per cent of the estimated birth weights fell within plus or minus one-half pound of the actual birth weight.

In 1954, Johnson and Toshach¹³ reported their clinical method and findings in 200

cases. They observed the height of the fundus to be 34 cm. with an average-sized baby of 7 pounds, 8 ounces in utero with the presenting part at station 0. Measurements more or less than 34 cm. indicated a baby weighing $5\frac{1}{2}$ ounces per centimeter more or less than $7\frac{1}{2}$ pounds. They used a simple correction factor for stations other than 0 and for obesity (weight over 200 pounds). By means of this method, they reported 50.5 per cent of estimated weights within three-fourths pound of the actual birth weight.

Methods and results

Since no one method appeared entirely satisfactory, we decided to study the problem further. We began by evaluating 200 sets of obstetrical films taken within one week prior to delivery in order to learn whether any of several skeletal evaluations might offer a solution. Not all films could be

utilized for every method investigated. Some had to be discarded because of roentgenologic error, fetal motion, abnormal presentation, etc. All patients were delivered within 7 days after roentgenologic examination, and all presentations other than vertex were excluded from this study. All films were taken with the patient in the supine position on the 90 degree apparatus table devised by Hodges. As stated earlier, this table consists of a motor-driven reciprocating Potter grid and an x-ray tube which are attached to a cradle mounted beneath the 24 by 84 inch top of a specially built x-ray table which has a 6 by $23\frac{1}{2}$ inch notch cut into its right side to receive the grid used in exposing the lateral film. The grid-tube assembly may be rotated so that the tube lies above and the film below for a frontal film view or so that the radiation is directed parallel with the floor for the lateral

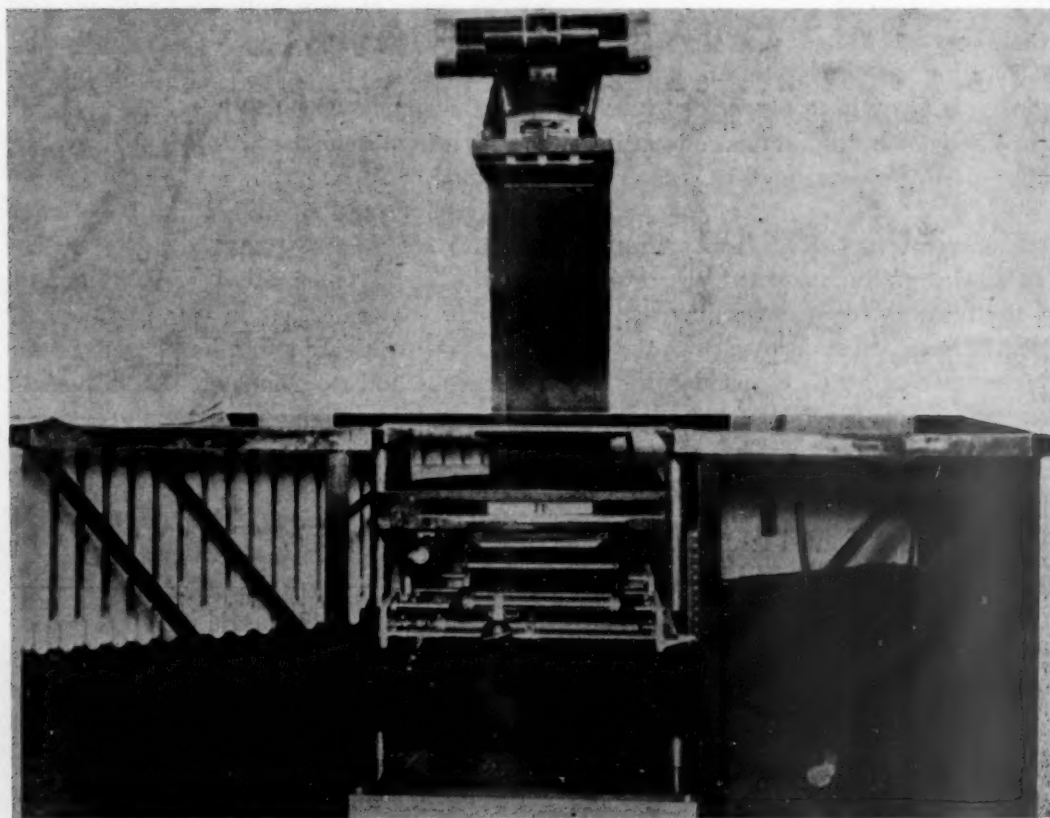


Fig. 1. The 90 degree apparatus arranged for frontal film. The cradle has been rotated so that the tube is above, grid below—preparatory for the making of the frontal film. Before the film is made, the cradle will be moved upward until its top is pressed against the under-surface of the table top. (From Hodges, P. C., and Nichols, R. L.: *Radiology* 53: 238, 1949.)

projection (Figs. 1 and 2). In this position, the grid may be moved inward toward the midline of the table or outward away from that line, and the amount of such movement is indicated on the H (horizontal) scale. The position of the grid on the V (vertical) scale was not significant in this study.

The obstetric routine included an anteroposterior and lateral film of the abdomen and pelvis (14 by 17 inches) and a lateral film of the pelvis only (10 by 12 inches). This series of three exposures has been used in this department since 1951 for all obstetric roentgenography with continued satisfaction. The x-ray tube-film distance was fixed at 36 inches in both planes. While x-rays were not ordered for all patients, all films obtained were evaluated irrespective of the primary indication for the roentgenologic examination.

While this study was primarily a roentgenologic approach to the problem, some clinical methods were also evaluated. Ten methods or combinations thereof were studied. Since no accurate technique for determining fetal weight had been previously reported, every conceivable approach was considered and evaluated. The method to be described in detail was the most accurate. Unfortunately, it does not fulfill the prerequisites set down by us at the beginning of this work.

Such things as height and weight of the patient, station of the presenting part, the symphysis-table height with the patient in the supine position and the object-film distance were found to be of no importance. However, the accuracy of the measurements increased when the presenting part was in a direct transverse position. The head presented in a left or right occipitotransverse position in 85 per cent of the cases.

For sake of clarification, each technique investigated will be considered separately.

A. Minor considerations.

1. Width of fetal subcutaneous fat line.

The width of the fetal subcutaneous fat line was helpful in gaining an impression of over-all size but did not reflect total fetal

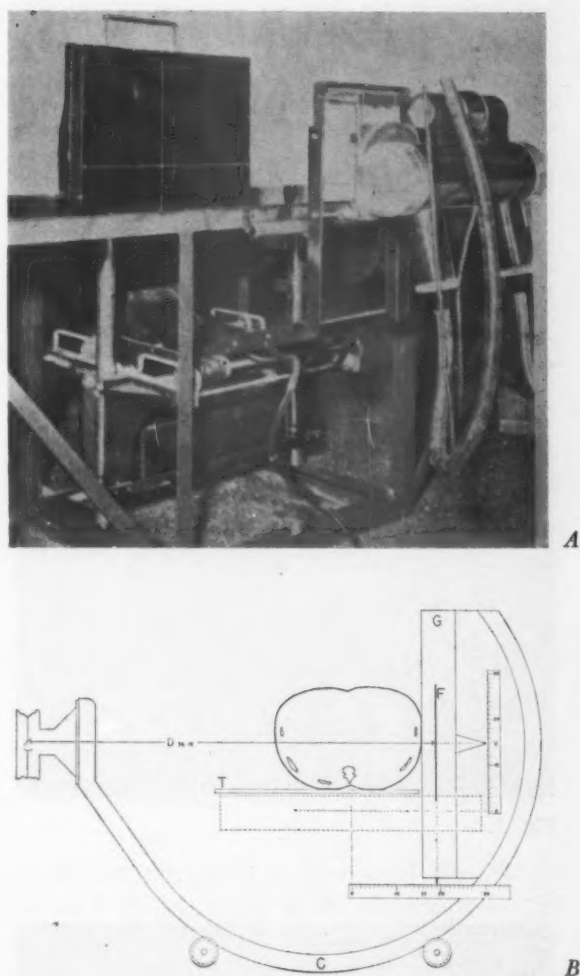


Fig. 2. A, The 90 degree apparatus arranged for lateral film. Cradle rotated into position for the making of the lateral film. B, Geometry of lateral film. Schematic elevation of apparatus with cradle (C) rotated so that the grid (G) is pressed against the side of the patient and the longitudinal axis of the lateral film (F) lies midway between the table top (T) and the anterior surface of the patient's body. The H scale indicates the distance between the sagittal plane of the body and the plane of the lateral film (the d of the midline structures in the lateral film). The V scale indicates the distance between the longitudinal axis of the lateral film and the plane that presently will be occupied by the frontal film (shown in dotted lines in the diagram). (From Hodges, P. C., and Nichols, R. L.: Radiology 53: 238, 1949.)

weight with useful accuracy. Furthermore, the fetal fat line can be confusing if edema is present as in erythroblastosis fetalis, diabetes, or syphilis. The average width of the subcutaneous fat line was 3 mm.

2. Length of femora and other long bones.

The length of the femora and other long

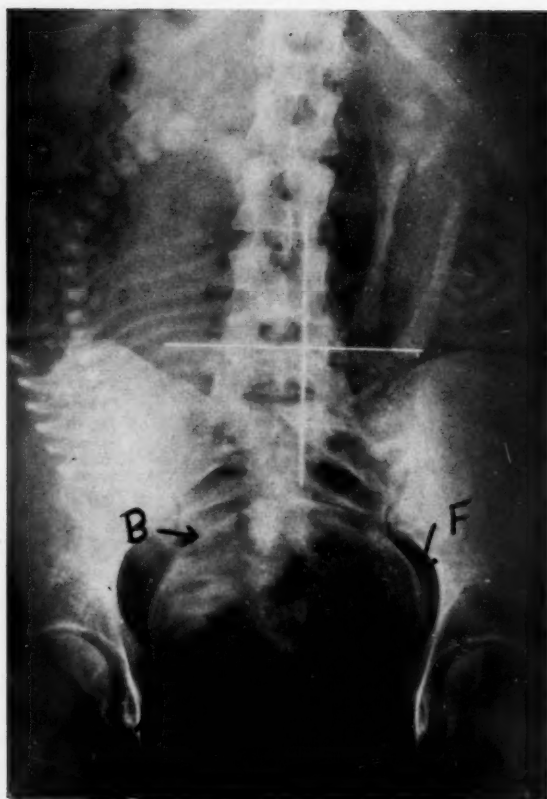


Fig. 3.

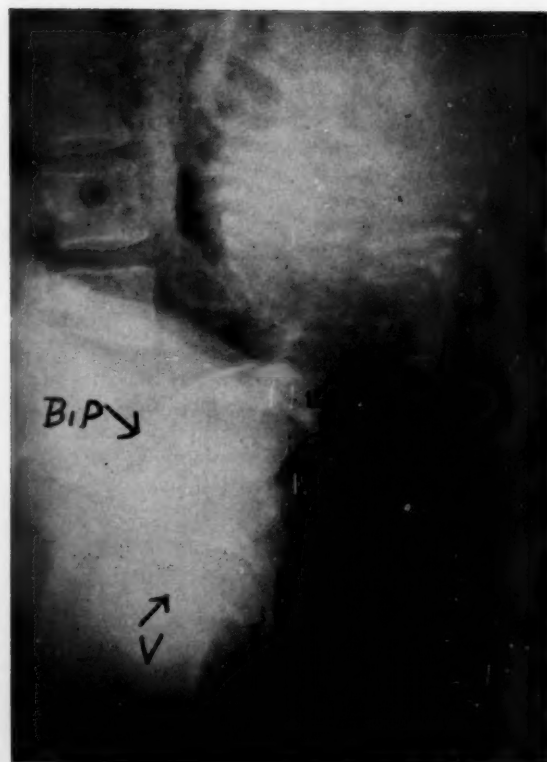


Fig. 4.

bones was of no value since a true anteroposterior and lateral view of these bones could not be consistently obtained.

3. *Size of vertebrae.* The body of L-1 of the fetal spine was measured longitudinally and transversely in the anteroposterior and lateral films. These measurements did not reflect fetal size or weight. Such measurements were not considered to be of value because of the tremendous variability of the fetal position in utero.

4. *Density of the fetal cranium or calvarium.* The density of the fetal cranium was measured with a densitometer but this, too, proved to be of little value since the slightest change in position of the instrument altered the reading significantly. Such readings were further complicated by the amount of soft tissue overlying the point on the cranium to be measured. Although inaccurate for weight estimation, densitometer readings did confirm the well-known fact that density of the cranial bones increases as the infant approaches term.

5. *Nomograms.* Nomograms were employed using various combinations of measurements, but no statistically significant pattern could be obtained.

B. Major considerations.

1. *Shortest and longest diameters of the fetal head on the lateral film.* The shortest and longest diameters of the fetal head on the lateral film were obtained irrespective of the position of the fetal head without regard to the anatomical point on its perimeter. These measurements could not be related to fetal weight.

2. *Shortest and longest diameters of the fetal head on the anteroposterior film.* The shortest and longest diameters of the fetal head on the anteroposterior film were likewise obtained with similar negative results. The summation of the measurements in 1 and 2 did not provide a helpful relationship to fetal weight.

3. *Shortest and longest diameters of an ellipse drawn around the fetus on the lateral film.* These measurements were thought to reflect the over-all volume of the infant but they proved to be of no real value as an

accurate index of fetal weight. Diameters were also recorded for an ellipse of the *body* of the fetus with similarly unsatisfactory results.

4. *Length of the fetal spine on the anteroposterior film.* The length of the spine on the anteroposterior film was measured from the tip of the sacrum to the base of the skull but varied markedly because of the fetal position and therefore provided no useful information regarding fetal weight.

5. *Clinical methods.* The clinical methods as described in the review of the literature were also investigated, but our results were both inconsistent and inaccurate.

6. *Evaluation of the specific diameters of the head from the anteroposterior and lateral films.* In another study of the anteroposterior and lateral films, 4 end points were identified. On the anteroposterior film, the occipitofrontal (OF) and the basivertical (BV) diameters were measured. Similarly, on the lateral film, the biparietal (BiP) and the basivertical (BV) diameters were obtained (Figs. 3 and 4).

In evaluating the anteroposterior film, the basivertical diameter is measured from the base of the fetal skull to its vertex. This diameter remains constant irrespective of the position of the head, i.e., as the head rotates through a 360 degree arc (without flexion or extension) the basivertical diameter will remain fixed. The occipitofrontal (OF) diameter of the fetal head is measured and is self-explanatory. One-half centimeter is *added* to the occipitofrontal diameter for every 45 degree rotation of the occiput from the transverse position to increase the accuracy of the measurement since the oblique positions do not give true occipitofrontal measurements.

In evaluating the lateral film, the basivertical diameter of the fetal head is again measured and remains fixed as described above. The biparietal diameter of the fetal head is measured and is self-explanatory. In further assessing the lateral film, the horizontal (H) scale and the position of the occiput must be considered. In dealing with the H scale, which indicated the distance

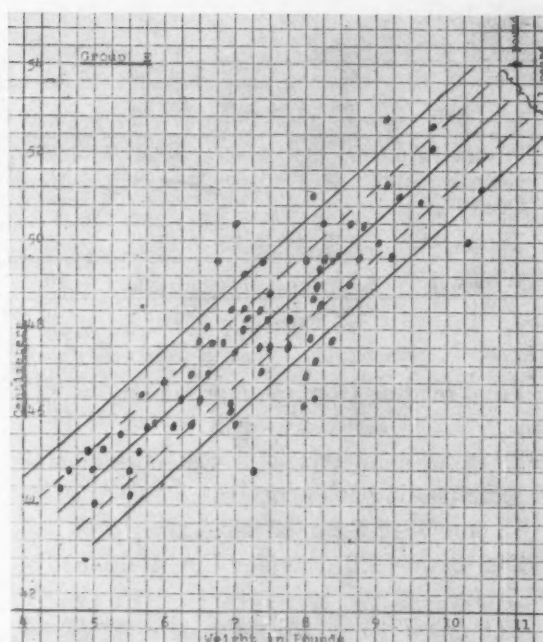


Fig. 5. Graphic representation of measurements taken for Group E (summation of the biparietal and basivertical diameters from the lateral film and the occipitofrontal and basivertical diameters from the anteroposterior film) in centimeters as plotted against the known fetal weight in pounds.

from the midpelvis to the x-ray film as recorded on the x-ray table, a reading of 20 inches is considered median. One-half centimeter is *subtracted or added*, as necessary, to the final figure for every one-inch deviation from this point on the H scale. Likewise, 0.5 cm. was *subtracted* from the biparietal diameter for every 45 degrees' rotation of the fetal head from the transverse position to give a true biparietal reading. In addition to being simple, these correction factors become necessary in only 15 per cent of the cases since 85 per cent of all cephalic presentations are in the occipitotransverse position.

EXAMPLES.

1. OLA position and H scale reading of 21 inches with biparietal diameter of 12 cm. and basivertical diameter of 11.5 cm.

$$12 + 11.5 = 23.5 \text{ cm.}$$

$$23.5 \text{ cm.} - 0.5 \text{ cm. (for OLA position)} = 23.0 \text{ cm.}$$

$$23.0 \text{ cm.} - 0.5 \text{ cm. (for H scale reading—head is greater distance from film at 21 inches than at 20 inch reading)} = 22.5 \text{ cm.}$$

Table I

	Group A		Group B		Group C		Group D		Group E	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Within ½ pound	43	57	42	56	38	51	31	41	46	61
½ to 1 pound	16	21	16	21	14	18	26	35	16	21
Over 1 pound	16	22	17	23	23	31	18	24	13	18
Total	75	100	75	100	75	100	75	100	75	100
Within 1 pound	59	78	58	77	52	69	57	76	62	82

Final reading from the lateral film = 22.5 cm.

2. Same diameters with OA position and H scale reading at 18 inches.

12 cm. + 11.5 cm. = 23.5 cm.

23.5 cm. - 1.0 cm. (for OA position) = 22.5 cm.

22.5 cm. + 1 cm. (for H scale reading) = 23.5 cm.

Final reading from lateral film = 23.5 cm.

The results of the various measurements accumulated from both the anteroposterior and lateral films and the combinations thereof were plotted graphically against the known fetal weight in pounds as indicated in Fig. 5 which is from Group E below. These data are representative of the 75 sets of film that were technically satisfactory and applicable to this portion of the study.

Table I is a compilation of the various measurements for each group taken from the anteroposterior and lateral film views when subjected to graphic evaluation (not all graphs are included). The 5 groups are as follows:

GROUP A. BIPARIETAL DIAMETER FROM THE LATERAL FILM. In review of the 75 cases, 57 per cent of the evaluations were within one-half pound of the known birth weight whereas 78 per cent were within 1 pound of the birth weight.

GROUP B. SUMMATION OF BIPARIETAL AND BASIVERTICAL DIAMETERS FROM THE LATERAL FILM. In this group, 56 per cent of the evaluations were within one-half pound of the known birth weight whereas 77 per cent were within 1 pound of the birth weight.

GROUP C. SUMMATION OF THE OCCIPITOFRONTAL AND BASIVERTICAL DIAMETERS FROM

THE ANTEROPOSTERIOR FILM. In this group, 51 per cent of these evaluations were within one-half pound of the known birth weight whereas 69 per cent were within 1 pound of the birth weight.

GROUP D. SUMMATION OF BIPARIETAL AND BASIVERTICAL DIAMETERS FROM THE LATERAL FILM AND OCCIPITOFRONTAL DIAMETER FROM THE ANTEROPOSTERIOR FILM. In this group, 41 per cent of the evaluations were within one-half pound of the known birth weight whereas 76 per cent were within 1 pound of the birth weight.

GROUP E. SUMMATION OF THE BIPARIETAL AND BASIVERTICAL DIAMETERS FROM THE LATERAL FILM AND OCCIPITOFRONTAL AND BASIVERTICAL DIAMETERS FROM THE ANTEROPOSTERIOR FILM. In this group, 61 per cent of the evaluations were within one-half pound of the known birth weight whereas 82 per cent were within 1 pound of the birth weight (Fig. 5).

It is interesting to note that there is only a 4 per cent increase in accuracy in Group E when compared to the evaluations in Group A even though there is a marked difference in mensuration technique.

It is therefore concluded that the most accurate results in this study were obtained when the biparietal and basivertical diameters from the lateral film and the occipitofrontal and basivertical diameters from the anteroposterior film were added together and plotted against the various known fetal weights. The original premise, however, was to devise a method to determine fetal weight in utero within one-half pound of the actual birth weight in 85 per cent of the cases. None of these evaluations achieved this premise.

Comment

It has long been thought that a more accurate evaluation of the intrauterine fetal weight would be advantageous in the management of obstetric patients. In our clinic, all obstetric x-ray films obtained during the week are discussed in conference with reference to the specific questions asked by the attending obstetrician requesting the films. The fetal weight is frequently estimated at this time since obstetric roentgenography for this purpose only is not employed routinely.

A review of the literature indicates that no truly accurate technique for evaluating intrauterine fetal weight exists. Information on the width of the subcutaneous fat line, the length of the femora and other long bones, the size of the vertebrae and the density of the fetal cranium was accumulated and evaluated. In addition, various diameters of the fetal head in both anteroposterior and lateral films were collected. Since the fetal head is *relatively* proportional in size to the body in normal infants it was thought that cranial measurements would be of value in reflecting the over-all size of the fetus.

After this material was subjected to graphic interpretation, it was apparent that no one factor could be considered an accurate index of fetal weight. Although not particularly accurate, the summation of the biparietal and basivertical diameters from the lateral film and the occipitofrontal and basivertical diameters from the antero-

posterior film in our hands permitted closer approximation of fetal weight than any other combination of roentgenographic evidence. As indicated in Table I, 82 per cent of the determinations were accurate within one pound of the actual birth weight whereas only 61 per cent of them were accurate within one-half pound of the birth weight.

One can only conclude that new and different techniques are needed for the accurate evaluation of intrauterine fetal weight.

Summary

1. The importance of fetal weight in utero as it pertains to the current evaluation of the obstetrical patient is discussed.

2. A review of the literature uncovered no accurate method for determination of fetal weight in utero.

3. Several methods for evaluating fetal weight in utero, based on a study of 193 cases, are presented.

4. A new method is introduced which uses the summation of the biparietal and basivertical diameters from the lateral obstetrical film and occipitofrontal and basivertical diameters from the anteroposterior obstetrical film taken on the 90 degree apparatus x-ray table devised by Hodges.

5. The relative accuracy of this method, however, does not fall within the accepted range for determining fetal weight in utero.

6. It is hoped this report may stimulate renewed interest in this problem.

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Evaluation of body and organ weights in perinatal pathology

II. Weight of body and placenta of surviving and of autopsied infants

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WITH increasing refinement in the study of the fetal aspects of pregnancy and child-birth the availability of normal standards becomes more and more important. The weight of the placenta, and of the body and internal organs of the newborn are among the readily accessible data and much can be learned from their proper interpretation. The present report presents those data which may be obtained from all newborn infants. Information on survivors will be contrasted with that on autopsied infants. This supplements our previously reported⁶ standards of organ weights which are, of course, only available from autopsies. Emphasis on standards based on gestational age and the knowledge of the normal range of values seems to us to be particularly important.

Average weights of newborn infants and placentas have been reported in the literature. They will be referred to later in comparison with the present data. We have added the standard deviation calculated in

the usual manner, in order to give an indication of the normal range.

Material and methods

The following data are derived from 1,232 consecutive single births resulting in infants discharged alive. All placentas were examined by us and weighed after removal of blood clots, and trimming the membranes and cord within 1 cm. of the placenta. Data on autopsied infants were obtained from the series of cases used in the previous study of organ weights⁶; the figures on body weight in relation to gestational age are, therefore, identical with those previously given. It would have been desirable to evaluate the birth weight of these same infants, but this information was not available in a sufficient number of cases. Autopsy material was made available for study by several colleagues in other hospitals as acknowledged in the previous report.⁶ Many autopsy reports do not include the weight of the placenta; it was available in 517 cases. The weight ratios of placenta : infant, sometimes referred to as placental coefficient, are derived from the mean values.

The figures indicating weight and age groups at the head of the columns in Tables I and II are median values. Individual data were grouped so that each case was allocated to the nearest value. Weights or gestational ages exactly halfway between two

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groups were allocated to the higher one. This creates a minor difficulty in the data classified by gestational age because figures for surviving and autopsied infants were not obtained in exactly the same manner. Body and placenta weights of surviving infants were classified by stated gestational age known by days, and the numbers of weeks at the head of the columns are, therefore, true median values for the respective groups. In the autopsy material information was available only by weeks in the majority of instances, and then grouped in 2-week categories. Each category of gestational age is a combination of data of that particular week and the previous one, and therefore a median gestational age of one half week less than indicated. A correction for this deviation by means of interpolation was made for the data shown in Table III and Figs. 1 to 3.

Results

The data represented by mean and standard deviation are given in Tables I and II; weight ratios and increments are calculated for the mean only. The mean values and ratios are shown in the form of graphs in Figs. 1 to 3; these also include comparable data from the literature and curves of the increase in body weight, expressed as per cent of the preceding lower value.

A comparison of the body weights shows consistently and considerably higher values for birth weight of survivors than for body weight at autopsy. The difference is in many groups of an order of magnitude similar to one standard deviation. The following explanations of this difference might be considered; these are not mutually exclusive, but probably all contribute to the total difference. Weights at autopsy were determined after a period of extrauterine life varying from 0 to 3 days (the arbitrary limit); most liveborn infants lose weight during the neonatal period. In addition there is a period of at least a few hours between death and autopsy, and it is common experience that bodies lose weight during this time, presumably through evaporation

of water from the body surface or oozing from orifices. Macerated stillborn infants in whom this oozing may assume great proportions are not included in this material. Third, it is possible that a significant number of infants dying during the perinatal period are actually smaller by birth weight than the survivors of comparable gestational age. As was previously stated, one of the groups of infants excluded from the present autopsy material consisted of those in whom diagnosis of intrauterine malnutrition was made prior to this study. This is a small group of severely affected infants from our own recent material. Less conspicuous cases were not recognized by us, and in the material from other institutions this diagnosis was hardly ever made. It is, therefore, likely that many such cases are included here and, since their mortality may well be higher than average, they may affect the autopsy group more than that of the survivors. Finally, the two sets of data were calculated in a slightly different man-

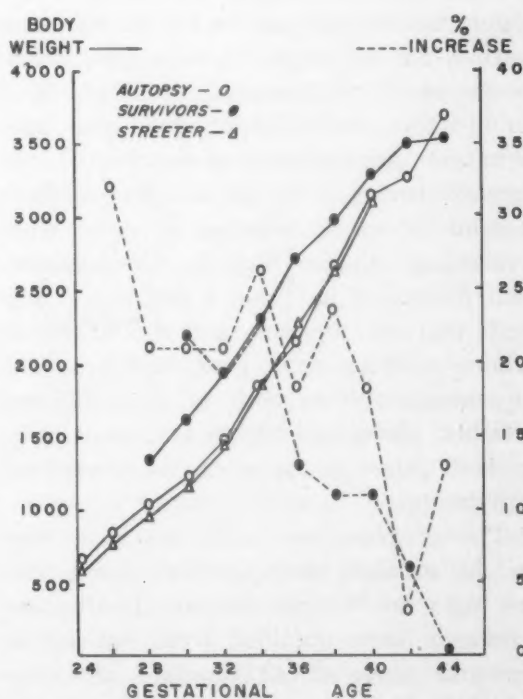


Fig. 1. Mean of body weight at autopsy and birth weight of survivors, by gestational age groups. Streeter's¹⁸ data are shown for comparison. Increase in body weight is given in per cent of preceding lower weight.

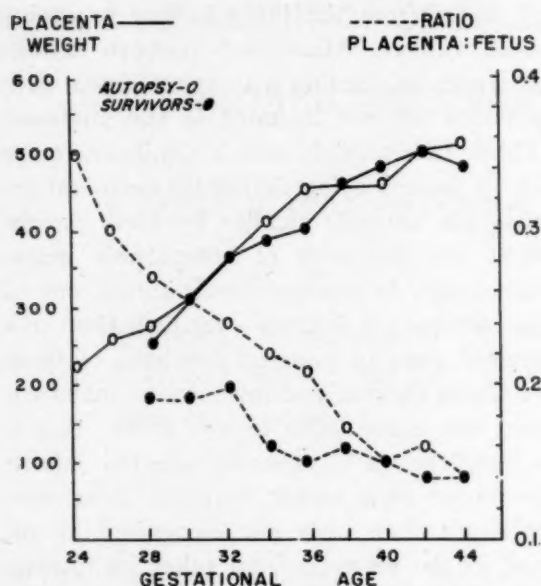


Fig. 2. Mean of weight of placenta and ratio of placenta to body weight, by gestational age groups.

ner as indicated above, and the gestational ages given for infants on whom autopsies were done are actually one half week less than those of survivors. If one were to correct for this discrepancy by adding to the values for autopsies one fourth the difference against the next higher group, each should be increased by approximately 50 grams up to 30 weeks, and 100 grams for higher ages. Whatever the explanation may be, the difference between the two series of body weights is worth keeping in mind when evaluating autopsy findings. One observation illustrated in Table I and Fig. 2 suggests that the survivors and the infants on whom autopsies were performed are actually comparable in spite of their different weights: placental weights are very similar in both series for most of the gestational age groups.

The normal range of values in relation to the standard deviation calculated from our data merits brief mention. If all measurements were obtained from normal infants, a range of ± 2 standard deviations which includes approximately 95 per cent of the cases might properly be considered as normal. However, our figures obtained from autopsy material are not necessarily representative of normal, even though a few

groups of striking abnormalities have been excluded. It was therefore suggested⁶ that in that material a range of ± 1 standard deviation, including approximately two thirds of all values used, might come closer to the limit of what is truly normal. This does not apply to data on surviving infants who are presumably normal with but few exceptions. This suggestion is not based on compelling evidence, and the reader should feel free to use the present data in any other manner. The statistical significance of the comparison of any given material with our data depends on the number and scatter of values being compared.

Data on the percentage increase in body weight (Fig. 1) and on the weight ratio of placenta and fetus (Tables I and II, Figs. 2 and 3) are presented for the sake of completeness; they confirm the well-known trends. It will be noted that the trends of growth of body and placenta change markedly when pregnancy proceeds well beyond term. The mean values for weight of both body and placenta are practically the same at 42 and 44 weeks (Tables I and III).

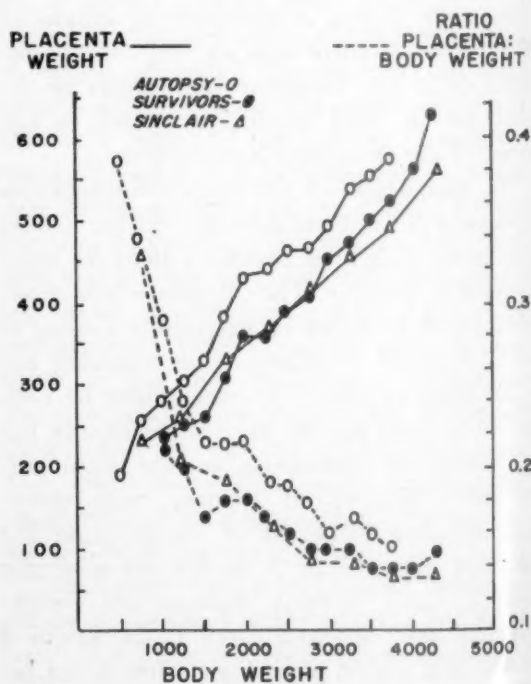


Fig. 3. Mean of weight of placenta and ratio of placenta to body weight, by groups of given body weight. Sinclair's¹⁵ data are shown for comparison.

Table I. Weight of body and placenta (grams) by gestational age (mean \pm standard deviation)

	Gestational age (weeks from LMP)										
	24	26	28	30	32	34	36	38	40	42	44
<i>Body weight</i>											
Birth weight of survivors			1,333	1,625	1,928	2,380	2,705	2,990	3,318	3,508	3,513
			± 405	± 550	± 438	± 483	± 500	± 383	± 438	± 455	± 360
Weight at autopsy	638	845	1,020	1,230	1,488	1,838	2,165	2,678	3,163	3,263	3,690
	± 240	± 246	± 340	± 340	± 335	± 530	± 600	± 758	± 595	± 573	± 800
<i>Placenta weight</i>											
Survivors			256	310	375	389	407	469	488	507	497
			± 71	± 71	± 80	± 80	± 93	± 88	± 88	± 96	± 100
Autopsy	225	256	277	303	362	410	453	465	469	508	518
	± 69	± 74	± 62	± 69	± 79	± 92	± 76	± 74	± 82	± 80	± 111
<i>Ratio, placenta : fetus</i>											
Survivors			0.19	0.19	0.20	0.16	0.15	0.16	0.15	0.14	0.14
Autopsy	0.35	0.30	0.27	0.25	0.24	0.22	0.21	0.17	0.15	0.16	0.14
<i>No. of cases</i>											
Survivors			9	13	11	23	63	225	555	296	112
Autopsy	108	143	139	148	150	104	87	102	220	112	42

There is also a change in the trend of weight ratio of placenta and fetus when fetal weight reaches about 4,000 grams. The previous trend characterized by a gradual lowering of the coefficient changes to one in which the latter remains the same. This appears in the curve of placental weight by body weight (Fig. 3) as a change to a steeper slope. The explanation may well be that the mean gestational age of fetuses weighing 4,000 grams and over is about the same. (See also Gruenwald and Minh,⁶ Table I, for a similar trend in autopsy material.) Some difficulties in evaluating these categories may be due not only to the relatively small numbers of cases available, but also to the possibility that the highest weight groups contain a significant number of infants resulting from pregnancies in women with unrecognized diabetes and prediabetes, whereas the highest age groups may contain a mixture of infants who continue to grow properly in utero past term, and others whose growth slowed to a varying extent as a result of relative placental insufficiency.

In evaluating the size of the placenta in relation to the infant, one may in certain cases have to choose between several possible interpretations. This occurs when there

is a discrepancy between body weight and gestational age. In an infant markedly underweight for the stated gestational age, one may find a ratio of placenta to body weight appropriate for the gestational age, but significantly low for a normal infant of that body weight. The weight of the placenta will then be too low, both for the gestational age and for the body weight (if the infant were a "normal" premature). Only the consideration of other pertinent data will enable one to select the proper manner of evaluation.

Comment

For the purpose of comparison with the present data on body weight, figures reported by others must be divided into three groups: those covering all births, those relating to surviving infants only, and those referring to cases of perinatal death only. Most authors have based their calculations on all births (including stillbirths and neonatal deaths)^{4, 7, 9, 11, 13, 21} or all live births (including neonatal deaths).^{12, 19} Some have not stated the exact nature of their material.^{17, 20} Almost all these data are in essential agreement with each other and with our figures in the range of 34 weeks and

Table II. Weight of placenta by groups of given body weight (grams)

	Body weight						2,000
	500	750	1,000	1,250	1,500	1,750	
Placenta weight							
Survivors			222 ± 51	253 ± 58	256 ± 63	319 ± 56	354 ± 71
Autopsy	193 ± 57	253 ± 60	288 ± 58	309 ± 61	328 ± 75	384 ± 83	434 ± 72
Ratio, placenta : fetus							
Survivors			0.22	0.20	0.17	0.18	0.18
Autopsy	0.39	0.34	0.29	0.24	0.22	0.22	0.22
No. of cases							
Survivors			8	8	8	8	20
Autopsy	105	85	58	37	32	24	29

over. Lubchenco and associates¹² report somewhat lower weights at term, and Wolf-ram²¹ higher ones. If one follows the data based on all births in the direction of decreasing gestational age, one notes a gradual change from agreement with our figures for survivors toward our figures obtained at autopsy.^{7, 12, 13, 20, 21} This is to be expected since mortality increases with decreasing gestational age. There remains a group of authors whose figures in the lower viable range, about 32 weeks, are considerably higher than those just mentioned as well as our own.^{4, 9, 11, 19} According to these workers, the mean birth weight at 32 weeks ranges about 2,300 grams. Why several authors should arrive at these obviously very high weights is unknown to us. Both Taback's¹⁹ and Little's¹¹ series of cases are small in the area in question, and in Little's group the standard deviations are very high. The only data based entirely on stillbirths are those of Streeter,¹⁸ which agree well with ours (Fig. 1). Kloosterman and Huidekoper¹⁰ have compiled data from the literature and, as might be expected, their lower limits agree with our autopsy values, and the higher ones approach ours on survivors.

In evaluating the weight of the placenta, one must remember that it is subject to two kinds of variations which are partly independent of one another, namely, one related to the size of the infant and the other related to gestational age. Ideally, placental

weight should be determined by weight groups for each group of similar gestational age. This has not been feasible, and as a substitute one may consult the ratio between fetal and placental weight as given in Tables I and II, and Figs. 2 and 3. It has not been possible to calculate ranges of these ratios since the highest fetal weights do not necessarily correspond to the highest placental weights, etc. It would be necessary to calculate the ratio for each case, and this has not been done. This question of the relationship between fetal and placental size bears on the old problem whether the size of the fetus determines that of the placenta, or vice versa, or whether both are determined jointly as parts of a common system, the ovum. It is certain that under normal circumstances the placenta has considerable functional reserve over and above the needs of the fetus. This makes the assumption of fetal size determined by the placenta untenable for normal pregnancies. If that assumption were true, all placentas should operate at, or very near, the limit of their functional capacity. The well-known variations in fetal : placental ratio consistent with normal progress of pregnancy suggest that neither of the two parts of the ovum controls the growth of the other. Only in instances of borderline or subnormal functional capacity of the placenta may growth of the fetus be limited by the placenta; this abnormal functional state results in patho-

Body weight	weight									
	2,000	2,250	2,500	2,750	3,000	3,250	3,500	3,750	4,000	4,500
19	354	358	395	417	451	475	500	528	563	667
56	± 71	± 66	± 69	± 74	± 78	± 81	± 81	± 85	± 77	± 79
84	434	437	463	464	492	540	558	575		
83	± 72	± 30	± 76	± 83	± 71	± 78	± 80	± 100		
18	0.18	0.17	0.16	0.15	0.15	0.15	0.14	0.14	0.14	0.14
22	0.22	0.19	0.19	0.18	0.16	0.17	0.16	0.15		
8	20	29	107	136	240	258	281	129	151	60
24	29	19	16	30	22	24	28	8		33

logic growth and, to a lesser extent, development of the fetus.

Information in the literature concerning placental weight is less extensive than that regarding the infant's weight. Since our weights were determined after removal of cord and membranes, we cannot compare them with those which include cord and membranes.^{1, 3, 8} The figures of McKeown and Record¹³ are so high that it may be assumed that they, too, were obtained without trimming cord and membranes, even though this is not stated. Sinclair^{15, 16} has studied placental weights in relation to body weight, and his data are entered in Fig. 3. They follow our figures on survivors except in the lowest weight group where they approach our data on autopsied cases. A similar trend is apparent in the placental coefficients reported by Wolfram.²¹ Little's¹¹ figures by gestational age are higher than ours in the same range in which his birth weight data are higher (see above). His placental coefficients agree well with ours obtained on survivors. A few coefficients given by Shanklin¹⁴ are intermediate between our autopsy and survivor figures. Adair and Thelander² divide their material into only two groups and the premature group contains only 18 cases; their data are therefore not comparable with ours.

The weight of the placenta should, in our opinion, be determined after removal of cord and membranes since the latter vary

greatly in weight and would thus introduce an error. Apart from extremes which can readily be recognized even by the inexperienced observer, variations in the weight of the placenta have not proved to be of great significance. In full-term pregnancy the placenta usually weighs approximately one seventh the weight of the infant; a number of instances were investigated in which the placenta weighed one tenth to one twelfth that of the infant and the great majority of the infants were entirely normal by all available standards, as of the time of their discharge from the hospital. It may be surmised that under normal circumstances the margin of efficiency of the placenta is greater than the variation in size, particularly when the fetus is adjusted to its placenta. However, determination of the weight of the placenta should be part of the examination since the weight must be considered as one of several factors affecting placental function and adequacy. Other significant factors may be brought out by gross and microscopic examination in conjunction with clinical data.

The present study is not intended to solve biologic or medical problems; it rather presents tools for evaluation of readily available information on newborn infants. In order to simplify their use, rounded figures are given in Table III. It is becoming increasingly clear that the proper examination of such abnormal infants as those with

Table III. Weight of body and placenta (grams) by gestational age (mean \pm standard deviation [sd]; rounded figures derived from smoothed curves)

Birth weight of survivors					Weeks from LMP	Weight of placenta*					Ratio placenta to fetus
-2 sd.	-1 sd.	mean	+1 sd.	+2 sd.		-2 sd	-1 sd	mean	+1 sd	+2 sd	
					24	90	155	225	295	370	1:2.9†
					25	100	165	235	305	380	1:3.1†
					26	110	180	245	315	390	1:3.3†
					27	120	190	260	325	400	1:3.5†
500	900	1,350	1,750	2,150	28	130	205	270	340	415	1:4.9
550	1,000	1,450	1,950	2,400	29	145	220	290	360	435	1:5.1
650	1,150	1,600	2,100	2,600	30	165	240	310	380	460	1:5.3
850	1,300	1,750	2,300	2,800	31	190	260	335	405	485	1:5.4
1,050	1,500	1,950	2,500	3,000	32	210	280	360	430	510	1:5.6
1,200	1,650	2,150	2,700	3,200	33	230	300	380	455	535	1:5.8
1,400	1,850	2,350	2,850	3,350	34	245	320	400	475	560	1:6.0
1,600	2,050	2,550	3,050	3,550	35	260	335	420	495	580	1:6.2
1,800	2,250	2,700	3,200	3,700	36	270	350	435	515	600	1:6.4
2,000	2,400	2,850	3,350	3,850	37	280	365	450	535	620	1:6.5
2,200	2,600	3,000	3,500	3,950	38	290	380	465	550	640	1:6.6
2,350	2,750	3,150	3,650	4,100	39	300	390	480	565	655	1:6.7
2,450	2,900	3,300	3,750	4,200	40	305	400	490	580	670	1:6.8
2,550	3,000	3,450	3,850	4,300	41	310	405	500	590	685	1:7.0
2,600	3,050	3,500	3,950	4,400	42	315	410	505	600	695	1:7.1
2,600	3,050	3,500	3,950	4,400	43	315	410	505	600	695	1:7.1
2,600	3,050	3,500	3,950	4,400	44	315	410	505	600	695	1:7.1

*Weight of the placenta is not significantly different in survivors and perinatal deaths. Both groups are therefore combined, and this accounts for the data from 24 to 27 weeks where the number of survivors alone is insufficient. Placentas were weighed without membranes and cord.

†Calculated from body weight at autopsy; others from birth weight of survivors; the former are generally higher than the latter.

hemolytic disease of the newborn, or those born to diabetic mothers depends on the possibility of relating measurements to normal standards for the respective gestational age rather than body weight alone. This holds true to an even greater extent for infants who have suffered intrauterine deprivation caused by placental insufficiency. The latter field of investigation stands and falls with proper correlations by gestational age. The present data should aid in such work and in efforts to get away from the estimation of maturity by weight alone. It is now becoming apparent that the infant who is underweight at birth presents a significant problem with suggestive evidence that brain damage may occur at least in severe cases.⁵ It is also becoming clear that the stated gestational age is more reliable than has been admitted, even in clinic populations who are not usually credited with great concern about details of their reproductive cycles and who are first interviewed fairly

late in pregnancy. Whenever estimation of maturity is possible at autopsy or upon detailed observation in the nursery, many discrepancies between birth weight and gestational age turn out to be real abnormalities based on abnormal growth rather than erroneous information due to incorrect dates.

Summary

Normal standards for birth weight of surviving infants, weight at autopsy of infants who died in the perinatal period, and weight of the placenta for both of these groups are presented. They are given in relation to gestational age and, in the case of the placenta, also by body weight. Significance and usefulness of this information are briefly discussed, particularly with regard to discrepancy between gestational age and birth weight.

Addendum. When classifying a group of surviving infants by means of the data in Tables I and III, we found that the distribution is not

as symmetrical as should be expected. The records from which the data in Table I were prepared apparently did not identify all neonatal deaths in the lowest gestational age groups, and are, therefore, more nearly representative of all live births in the area below 34 weeks of gestation. This may be advantageous since data based on survivors alone may give a distorted

view of the normal body weight, because mortality of the smaller infants within a group may be disproportionately high. In the area above 34 weeks our data agree well with those of Lindell (*Acta obst. et gynec. scandinav.* 35: 136, 1956) which show the difference between weights of surviving and dead infants based on birth weights throughout.

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Vitamin K administration and neonatal hyperbilirubinemia of unknown etiology

A double-blind study

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SINCE Allison's report¹ in 1955 of the production of hyperbilirubinemia in the newborn by the administration of sodium menadiol diphosphate (Synkayvit), this drug has been used with caution in the neonatal period. More recently the question has been raised as to whether or not the administration to the mother of vitamin K during labor could contribute to the frequency and severity of neonatal icterus.

Two problems would immediately appear to be involved: the dosage of vitamin K which is required to produce hyperbilirubinemia in the neonatal period, on the one hand, and the amount which the placenta will transmit to the fetus, on the other. With respect to the first of these questions, it should be noted that the dosages of water-soluble vitamin K (largely in premature infants) which have led to difficulty have been extraordinarily high^{2, 3, 4}; for example, the 6 babies reported on by Laurance² had received 100 mg. each within the first 4 days of life. Since blood levels of vitamin K cannot be measured directly, the question of placental transfer to the fetus

cannot be answered quantitatively. Taylor's⁵ study with C¹⁴-labeled vitamin K in the rat does not permit complete quantitation since the site and amount of dissociation cannot be determined accurately; certainly, however, not all of the material was found on the fetal side of the placenta.

In 1958 Lucey and Dolan⁶ reported an increased incidence of hyperbilirubinemia in premature infants whose mothers had received large doses of menadione sodium bisulfite (Hykinone). Seven infants with bilirubin levels between 21 and 47 mg. per 100 c.c. were reported on. No mention was made of the results of the Coombs tests in these infants.

Because of a real or apparent increase in neonatal jaundice in this hospital, it was decided to see if a 5 mg. intramuscular dose of vitamin K (Hykinone) to the mother during labor would be associated with hyperbilirubinemia in the neonate.

Patients and procedures

The study here reported was carried out on a double-blind basis. Two sets of ampules were stocked on the delivery room floor, one set labeled X and the other Y. The ampules in one set contained 2.5 mg. of vitamin K (Hykinone) each, while those in the other set contained normal saline.

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The selection of which patient was to receive X and which was to receive Y was based on whether the hospital registration number was odd or even.

No other change was made in the labor room procedure. Two ampules were administered to each mother in labor. If the mother was delivered in an hour or less after receiving the medication, the baby was given a single ampule (of the same code lettering as the mother's). In 8 instances in the X group and 3 instances of the Y group the time interval was too short and the baby also received medication under this policy.

The study was carried out on 533 consecutive patients, 266 of whom received one medication and 267 the other. From an obstetric viewpoint (age, parity, length of labor, intercurrent illnesses, etc.) the two groups were comparable. The records of all babies with clinical jaundice from this group were reviewed, and those with a hematological explanation for the icterus (major or minor blood incompatibility) were eliminated (21 cases or 3.9 per cent). There were 32 babies (6 per cent) remain-

ing with neonatal jaundice of undetermined etiology. The code as to which ampules contained vitamin K and which were blank was known only to the manufacturer until after the study was completed and these 32 cases had been summarized.

Results

Among the 266 patients who received vitamin K, neonatal jaundice of undetermined etiology was noted in 19 babies; among the 267 patients receiving the blank, neonatal jaundice of undetermined etiology was found in 13 babies. This difference is not statistically significant. The information concerning these two groups of jaundiced babies is shown in Tables I and II.

Considering the 19 cases of jaundice which occurred in the babies in the vitamin K group, the average peak bilirubin level was 17.6 mg. per cent and exchange transfusions were given to 4 infants. In 2 of the cases listed here, there was an Rh-negative mother with an Rh-positive baby; neither mother had demonstrable antibodies, and the Coombs tests were negative in

Table I. Nineteen infants whose mothers were given 5 mg. of vitamin K during labor

No.	Sex	Race	Birth weight (grams)	Maternal blood type and Rh	Fetal blood type and Rh	Coombs test	Age jaundice noted	Peak bilirubin and age (total direct) (mg. %)	Exchange transfusion
1	M	W	2,620	A-	A-	Negative	49 hours	14.5 -0.5 (5 days)	No
2	M	W	3,530	A+	A+	Negative	48 hours	14.3 -0.47 (3 days)	No
3	F	W	3,560	A+	O+	Negative	24 hours	20.9 -0.8 (3 days)	Yes
4	F	W	3,140	A+	A-	Negative	24 hours	24.6 -0.8 (4 days)	Yes
5	F	W	3,160	O+	O+	Negative	48 hours	25.4 - (5 days)	Yes
6	M	W	3,820	O-	O-	Negative	2 days	12.8 -0.6 (2 days)	No
7	M	W	2,430	A+	A+	Negative	2 days	21.6 -0.8 (5 days)	No
8	M	W	3,130	O+	O+	Negative	3 days	12.0 -0.6 (3 days)	No
9	F	W	3,140	O+	O+	Negative	2 days	12.0 -0.6 (3 days)	No
10	F	W	2,980	A+	A+	Negative	1 day	22.65-1.5 (4 days)	No
11	F	W	3,590	O-	O+	Negative	21 hours	13.8 -0 (3 days)	No
12	F	W	3,870	A+	A+	Negative	1 day	12.9 -0.5 (3 days)	No
13	F	W	2,770	A+	A+	Negative	2 days	16.38-0.47 (3 days)	No
14	F	W	3,140	B+	B+	Negative	2 days	12.4 -1.0 (2 days)	No
15	M	W	3,810	A+	A+	Negative	2 days	20.0 -0.5 (5 days)	No
16	M	W	3,440	O+	O+	Negative	5 days	18.0 -0.6 (5 days)	No
17	F	N	1,560	A+	O+	Negative	2 days	20.9 -1.6 (4 days)	No
18	M	W	1,840	A+	O+	Negative	2 days	18.0 -0.7 (5 days)	No
19	M	W	2,620	B-	O+	Negative	1 day	21.2 -0.7 (3 days)	Yes

Table II. Thirteen control infants whose mothers were given a placebo during labor

No.	Sex	Race	Birth weight (grams)	Maternal type and Rh	Fetal type and Rh	Coombs test	Age jaundice noted	Peak bilirubin and age (total direct) (mg. %)	Exchange transfusion
1	M	W	3,910	A+	A+	Negative	3 days	20.7-0.6 (7 days)	No
2	M	W	4,000	AB+	AB+	Negative	7 days	16.7-1.17 (7 days)	No
3	F	W	3,260	B-	O-	Negative	2 days	17.4-0.4 (4 days)	No
4	M	W	3,100	O+	O+	Negative	3 days	12.2-0.5 (4 days)	No
5	M	W	3,100	A+	O+	Negative	3 days	12.8-0.5 (3 days)	No
6	F	W	3,610	O+	O+	Negative	3 days	12.3-0.4 (3 days)	No
7	M	W	3,190	A+	O+	Negative	5 days	18.6-0.3 (5 days)	No
8	F	W	3,280	A+	A+	Negative	4 days	16.9-0.9 (2 days)	No
9	F	W	3,280	A-	A+	Negative	2 days	12.4- (2 days)	No
10	M	W	3,360	O+	O+	Negative	3 days	13.1-0.3 (4 days)	No
11	M	W	3,590	A+	A+	Negative	3 days	13.1-0.3 (4 days)	No
12	F	W	3,470	O-	O+	Negative	2 days	12.8-0.9 (5 days)	No
13	M	W	2,640	A+	A+	Negative	2 days	14.6-0.5 (3 days)	No

both. The 19 babies on this chart constitute 7.2 per cent of the original 266 babies born to mothers who received vitamin K. In 8 of these cases the baby had received 2.5 mg. of the medication under the policy cited above since the maternal medication preceded delivery by too brief a time.

The data from the cases of babies born to mothers receiving the blank injection and who developed neonatal jaundice of unknown etiology are summarized in Table II. The average bilirubin peak was 14.5 mg. per cent and no exchange transfusions were given. There were two circumstances in which an Rh-negative mother bore an Rh-positive child but in neither was there a positive Coombs test or a record of maternal antibodies. This group is 4.8 per cent of the original 267 babies born to mothers who received the placebo.

In comparing these two groups, it is well to review critically those factors which could introduce variables. For a baby to be listed in either Table I or Table II, three prerequisites had to be fulfilled: a bilirubin determination performed, a predetermined bilirubin level reached, and no explanation for jaundice discovered by standard tests. The decision to request bilirubin determinations rested with the individual private and staff pediatricians involved. This was a sizeable group and variability could have been

introduced on the basis of differing indices of suspicion. It has been our experience, however, that with the increasing ease of performance of the blood bilirubin determination the test is overused rather than underused. The finding of such levels as 2.8 mg. per cent and 4.4 mg. per cent, for example, among the records of these 533 babies would make it doubtful that many truly icteric babies were missed. The level of bilirubin selected to "qualify" a baby for inclusion in the tables was 12 mg. per cent for term and premature infants. However, the figures were recalculated with the dividing line as being 16 mg. per cent, and there was still no statistically valid difference between the two groups. The factors of the initial decision to obtain a bilirubin level and the milligrams per cent selected to represent jaundice are not believed to represent significant variables. We feel, however, that the number of exchange transfusions employed could not be considered a reliable index since during the period of this study the exchange transfusion facilities were under the direction of two different members of the staff, and the matter of personal taste and policy might have entered into the decision. One Mongoloid infant who had a bilirubin level above 20 mg. per cent did not receive an exchange transfusion.

Three additional babies developed bilirubin levels over 12 mg. per cent but were eliminated from consideration because an apparent explanation was readily available and they could not be classified as having jaundice of unknown etiology. Two of these infants were from the placebo group. One was diagnosed as having septicemia (peak bilirubin level 21.3 mg. per cent) and the other as having hemorrhagic disease of the newborn (peak bilirubin level 14.6 mg. per cent). The third infant had a bleeding dyscrasia. He was in the group treated with vitamin K and had a peak bilirubin level of 26.2 mg. per cent at 4 days of age.

The statement that the different frequencies of jaundice in the two groups "is not a statistically valid difference" cannot be interpreted as being identical with the statement "the administration of vitamin K has no effect on the development of neonatal icterus." It means only that the figures derived from a series of this size does not establish a positive etiological relationship; their failure to prove this does not prove the opposite.

There are other criteria which can be used to judge whether or not the vitamin K was associated with the appearance of neonatal hyperbilirubinemia. A bilirubin level of 20 mg. per cent is now universally considered to be a potentially dangerous level in relation to the development of kernicterus since the report of Hsia and associates⁷ in 1952. A scattergram of the 32 cases in which a level of bilirubin over 12 mg. per cent developed is presented in Fig. 1. Eight babies in the group treated with vitamin K reached a level of 20 mg. per

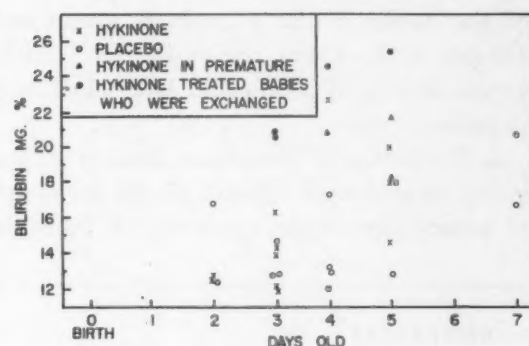


Fig. 1. A scattergram of 32 infants with bilirubin levels of 12 mg. per cent. Eight infants in the vitamin K (Hykinone) group have bilirubin levels of at least 20 mg. per cent and one infant in the placebo group has a bilirubin level of at least 20 mg. per cent.

cent or more. Two of these infants were premature by weight, but even excluding these there are 6 babies who reached this danger level whereas only one baby in the placebo group reached 20 mg. per cent or more.

During the period of this study 3 babies developed bleeding manifestations. One (first day) was from the vitamin K group and had a prothrombin level of 68 per cent. While the diagnosis is not completely established at the time of writing, it is probable that this child has hemophilia. Two of the babies in the placebo group bled (second day); one had a prothrombin level of less than 7 per cent and the other of less than 5 per cent. As controls, 6 babies—3 from the vitamin K group and 3 from the placebo group—were selected at random for prothrombin determinations and these results are shown in Table III. Not all babies deprived of vitamin K have prothrombin levels which drop to a dangerous point.

Conclusions

1. A double-blind study was performed in which 266 women in labor were given vitamin K (Hykinone) and 267 women in labor were given a placebo (saline). The incidence of jaundice of unknown etiology in the progeny of the two groups was compared.

2. The results indicate that 7.2 per cent

Table III. Prothrombin determinations performed in second and third day of life

Baby	Age (days)	Prothrombin level (%)	Medication
1	3	86	Vitamin K
2	3	65	Vitamin K
3	2	42	Vitamin K
4	3	21	Placebo
5	3	86	Placebo
6	2	70	Placebo

of the babies in the vitamin K group and 4.8 per cent of the babies in the placebo group developed a bilirubin level of 12 mg. per cent or more.

3. Excluding 2 premature infants in the group treated with vitamin K, the incidence of potentially dangerous levels of bilirubin

was five times as great in the vitamin K group as in the control group.

We wish to express our appreciation to Dr. George H. Berryman of Abbott Laboratories for providing the ampules of Hykinone and the matching ampules of saline.

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Dicephalus dipus tribrachius

Case report

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CONJOINED twinning is a rarity, the incidence being about 1:60,000 births.¹ Because of the scarcity of detailed anatomic descriptions of such anomalies we feel it is of interest to report a case of dicephalus dipus tribrachius we recently had the opportunity to study.

Conjoined twins, or diplopagi, are defined as twins that have some variety of anatomical union. In equal, or symmetrical, conjoined twins the duplicated parts are of equal or near equal size and configuration. In unequal, or asymmetrical, conjoined twins an incompletely developed part of a body (the parasite) is attached to a larger, more fully developed one (the autosite). Dicephalus dipus tribrachius is of the symmetrical variety and is a fetus with lateral union of the pelvis and thoraces, with 2 heads, 2 legs, and 3 arms.

Conjoined twinning is a common anomaly in lower forms of life. Witschi² reported it as a common occurrence in teleosts. He produced it experimentally in trout by transplanting a small part of primitive tissue into a blastopore lip. Multiplicity of the upper parts in this species is far more frequent than the duplication of the lower parts. Huxley and DeBeer³ reported its experimental production by Spemann in Triton by placing constricting bands around the early gastrula in the plane of symmetry. Patten⁴ reported

the spontaneous production of similar anomalies in chickens. Duplication varies in human beings from doubling of small areas of the face (e.g., frontal bone, nose, and palate) to the development of 2 complete individuals with a narrow anatomic union. There is, in fact, a complete gradation of lateral duplications which is well illustrated by Potter.¹ In human specimens, as in lower species, caudad doubling is much rarer than cephalad. Union also may occur back to back, face to face, vertex to vertex, or pelvis to pelvis. For purposes of general classification the suffix "pagus" (Greek root = fastened) is added to the anatomical term designating the region of fusion. According to this nomenclature, dicephalus dipus tribrachius is of the thoracoischiopagus variety.

It is generally accepted that conjoined twins are usually uniovular.^{1, 3, 5, 6} Aird⁷ calls attention to the facts that conjoined twins nearly always unite at identical parts of their external surfaces and that they are always of the same sex as good evidence to support this hypothesis. If fission of the ovum occurs before the embryonic disc is identifiable (at the inner cell mass stage) separate embryos with separate amnions develop. If two separate centers of axial growth develop on the embryonic disc, separate twins form within a common amniotic sac. If the centers of axial growth are not sufficiently separated on the embryonic disc it is theoretically possible that the intermediate area might be shared by both twins. Another possibility more generally accepted is that there is

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Fig. 1. Anterior view of the dicephalus dipus tribrachius monster.



Fig. 2. Posterior view of the dicephalus dipus tribrachius monster. Note the tail-like structure and the 9 fingered common hand.

partial fission of a single growth center on the embryonic disc, the location of the splitting determining the variety of conjunction. In symmetrical conjoined twins Potter¹ feels that fusion of dual axial growth centers is highly unlikely because fusion should, at times, at least, produce irregular distribution of parts instead of the bilaterally symmetrical arrangement which invariably occurs.

Aird^{7, 8} discussed the possibility that at least occasionally conjunction might occur in binovular twins. This would require, first, rupture of the amniotic partition and subsequent fusion of the embryos. He mentioned as evidence for this possible etiology the facts that (1) conjoined twins are not as identical as separate uniovular twins (2) conjunction of extensive degree is very commonly associated with asymmetry of internal organs, and (3) a case has been reported of a eunuch conjoined to a normal male.

The weight of evidence, however, strongly suggests that the vast majority of conjoined twins are uniovular in origin. In fact Aird's reasoning does not preclude the possibility of fission for it has been shown that with

one twin normal the other is more often grossly monstrous when twins are uniovular zygotic than when they are binovular.

History. The patient was a 28-year-old white woman with a family history of diabetes mellitus who, herself, had had diabetes for the past 6 years. Her only previous pregnancy was terminated by a cesarean section in 1957 at 32 weeks' gestation because of uncontrolled diabetes. A 2,890 gram female infant was delivered who is now living and well.

The patient's last menstrual period was Jan. 24, 1959, and the expected date of confinement Oct. 31, 1959. She had two episodes of spotting at the times of her expected menses in February and March. At her first prenatal visit in May, physical and laboratory examinations revealed no abnormalities. The uterus was enlarged to the size of a 22 weeks' gestation and the fetal heart rate was 110 per minute. She was taking 60 units of NPH insulin daily and the urine was sugar free.

In early July she was admitted to the United States Naval Hospital at Great Lakes, Illinois, because of several insulin reactions. The diabetes was moderately controlled with 60 units of NPH insulin and a 1,500 calorie low-salt diet. Insulin

had to be increased to 80 units per day in August but the patient continued to have glycosuria and was readmitted to the hospital in mid-September because of glycosuria and edema. The fetus was active, and the heart rate was recorded as 110 per minute. She responded well to chlorothiazide, 500 mg. twice a day and bed rest. The diabetes was under moderate control.

Delivery of the patient at 36 to 38 weeks by cesarean section had been planned but at 35½ weeks' gestation labor started spontaneously. A laparotrachelotomy was performed and conjoined twins were delivered. Weak cries were heard from each head and 2 heartbeats were audible. Poor attempts at respiration were made by each twin but both ceased breathing after about 30 minutes.

Pathologic examination.

General appearance. The body was that of a well preserved, 2 headed, 3 armed, 2 legged, white female infant weighing 2,800 grams and measuring 42 cm. crown to heel and 28 cm. crown to rump (Figs. 1 and 2). Both heads were normal in size and shape, the right having a frontal occipital circumference of 28 cm., the left 30.5 cm. The skull bones were normal on gross and x-ray examination (Fig. 3). A double vertebral column was present, each having pedicles and ribs on both lateral aspects. The spines were completely bifid. Many hemivertebrae were present in both lumbar regions and one hemivertebra was noted in the cervical region. The segmental distribution was slightly abnormal in that the twelfth thoracic vertebra of the right baby had a rib bridge to the first lumbar vertebra of the left. Between the 2 columns were vertebral ribs. Four scapulae and 4 clavicles were present. There were 2 sets of sacral vertebrae and one normal pelvis. The thoracic cages were fused laterally with one nipple for each chest. The circumference was 34.3 cm. at the nipple line. No distinct sternum was palpable. There was a single abdomen measuring 30.5 cm. in circumference at the level of the single umbilicus. The perineum was that of a normal female except for the presence of a soft tissue appendage 2.5 cm. in length and 0.75 cm. in diameter attached 2 cm. to the left of the midline posterior to the anus. It consisted of a firm connective tissue core covered by subcutaneous tissue and skin and contained an opening at the distal end of its ventral surface which admitted a probe for approximately 1

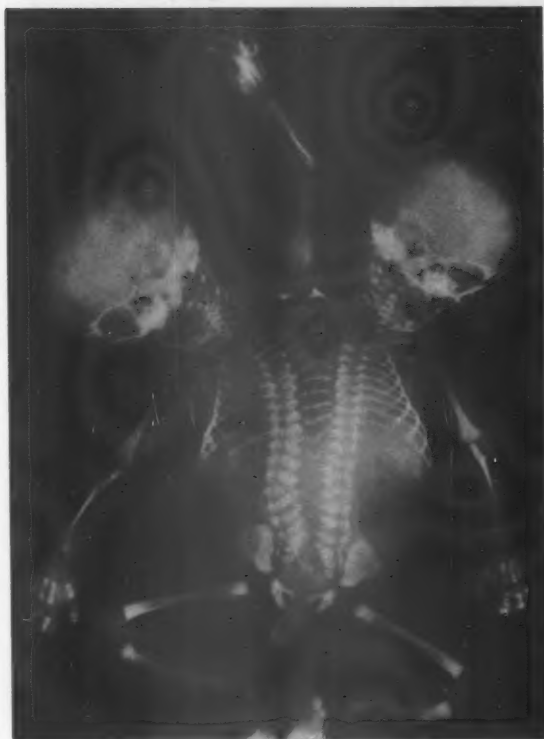


Fig. 3. Roentgenological picture of the monster showing the skeletal anomalies.



Fig. 4. A view of the chests and abdomen open. Note the two hearts, the stomach and liver lobe in the right chest of the right baby, and the large single fused liver.

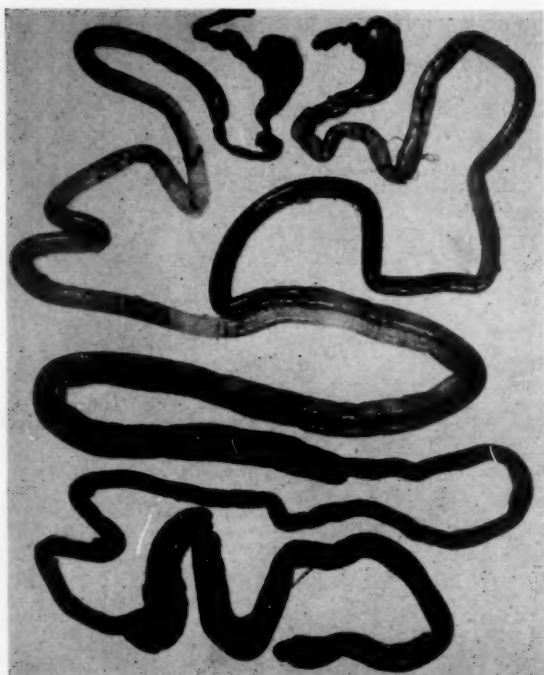


Fig. 5. The 2 gastrointestinal tracts. Note how the proximal thirds of each tract are completely separate, how the middle thirds run side by side, and how they fuse into a common single bowel at their distal one third.

cm. The lower extremities were normal. Each infant had one normal arm on its lateral aspect. A hyperabducted common third arm arose from the medial aspect of each infant at the line of fusion; it was slightly flexed and had very poor mobility. It consisted of a fused humerus, single ulna, 2 radii, and 2 sets of carpal bones. The common hand had 2 thumbs, 2 index, 2 middle, and 2 ring fingers, and a poorly developed common fifth finger. The two palms were fused at their ulnar aspect.

Head and neck. The head and neck on each side were entirely separate and the internal and external structures of each were normal. Both brains were normal.

Chest. The thoracic cage was composed of 2 vertebral columns connected by 12 pairs of ribs, each pair being separately fused in the midline. The posterolateral and anterior aspects of the thoracic cage were composed of 12 pairs of ribs which were the lateral set of ribs of each baby and which fused anteriorly to form a common sternum. There were 2 sets of mediastinums each containing a complete set of organs. Four pleural cavities were present, the medial being

separated by a fused pleural membrane. Two pericardial sacs were present.

Right thoracic cavity. A defect 5 cm. in diameter in the posterolateral aspect of the right diaphragm was responsible for the presence of the stomach, spleen, and a large portion of the liver in the right pleural cavity (Fig. 4). No hernial sac was demonstrated. The right lung was bilobed and hypoplastic. The left lung was trilobed and was of normal size. Both lungs were expanded. The heart was a four-chambered organ with a high interventricular septal defect 1 cm. in diameter and a patent foramen ovale. A single aortopulmonic arterial trunk emerged from the right and left ventricles, gave rise to 2 pulmonary arteries, 2 common carotid arteries, and 2 subclavian arteries, and continued as the descending aorta. The left subclavian artery provided the major blood supply to the common arm. After anastomosing with the small right subclavian artery of the left baby the arch of the aorta descended in the left side of the mediastinum. The left diaphragm was normal. The right jugular and subclavian veins joined and entered the right auricle separately from the joined left subclavian and jugular veins. The esophagus was normal in length and entered the abdomen through the esophageal hiatus.

Left thoracic cavity. Two pleural cavities were present. The diaphragm and both lungs appeared normal. The heart was a four-chambered organ with a high interventricular septal defect 1 cm. in diameter and a patent foramen ovale. The pulmonary artery arose from the right ventricle and supplied each lung. The aorta arose from the left ventricle and was extremely hypoplastic, measuring only 2 mm. in diameter. After giving off an innominate artery, a left subclavian artery, and a left common carotid, the aorta became more stenotic. It was joined by a widely dilated ductus arteriosus and then continued as the descending aorta in the left mediastinum. The inferior and superior venae cavae were normal. The esophagus entered the abdomen through the esophageal hiatus. The lungs were expanded.

Joined portion of the baby. The abdominal cavity was single and contained 5 c.c. of straw-colored fluid. The liver consisted of a fused organ weighing 146 grams with 2 separate extrahepatic biliary systems. There was one central falciform ligament and one ligamentum venosum. The right portion was smaller and had

its own caudate and quadrate lobes. In the hilum of each liver a portal vein, hepatic artery, and common bile duct could be identified. Each small intestine had an independent course for its proximal 78.5 cm. (Fig. 5). They then ran parallel within a common serosa for 68.5 cm. and finally united to form a single lumen for the distal 66 cm. The cecum was mobile. The ascending colon and appendix were normal. A redundant loop of transverse colon was attached to the midline of the posterior abdominal wall by a mesentery primum. The splenic flexure was not fixed to the posterior abdominal wall. The remainder of the bowel was normal and contained meconium. The aortas entered the abdominal cavity separately and fused to form a single vessel distal to the celiac axis. There was no duplication of the genitourinary system. Both kidneys were normal. Both ureters were of normal caliber and entered a normal bladder. The left adrenal was unusually large and weighed 9 grams; the right weighed 3.5 grams. The left adrenal was of approximately normal thickness but the surface area was considerably increased. The vagina, uterus, Fallopian tubes, and ovaries were normal.

Placenta. The placenta weighed 478 grams and measured 19 cm. in diameter. One amnion and one chorion were present. The fetal and maternal surfaces were normal. A single cord was inserted at the margin.

Microscopy examination. Microscopy studies revealed no histologic abnormality of any viscera. Both adrenal glands appeared to be of normal structure in spite of the difference in size. The gonads resembled normal ovaries. The perineal soft tissue appendage was covered by normal skin and contained an irregular cavity lined by squamous epithelium which was surrounded by hypoplastic erectile tissue. It was interpreted as a pararectal phallus.

Summary

1. A case of *dicephalus dipus tribrachius* is described in which 2 complete thoracic cavities and a single abdominal cavity were present. Several cardiac malformations are described in detail. A small phallus-like structure is described grossly and microscopically.

2. Conjoined twins are defined and classified.

3. The uniovular and binovular theories of etiology are presented.

4. The vast majority of evidence indicates a uniovular origin of conjoined twins.

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Genital anomalies in women

An evaluation of diagnosis, incidence, and obstetric performance

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THE history of the anomalous uterus is characterized by wide variations in medical thinking. Considered to be normal for 14 centuries, the bicornuate uterus was replaced by the uterus simplex following the engravings of Berengarius and Eustachius⁵ in 1514 and 1522. For the next 300 years, the anomalous uterus was not only considered rare but even incompatible with life. According to Miller,¹¹ Frankel cited the cases of Olliver and Bonnet as the first living adult patients with uterus didelphys in 1873 and many small series of collected cases were reported by the turn of the century. Attention turned to the gynecologic and obstetric complications associated with these anomalies. In general, only the more obvious malformations were recognized. Mild degrees of anomaly were diagnosed secondary to complications arising in them. As a result, the incidence of anomalies was considered quite low and their physiologic performance poor.

The incidence of anomalies of the uterus has been reported from 1:10 to 1:1,500.^{1, 3, 4, 6, 12, 14} This wide deviation is explained mainly by a lack of prospective diagnosis. Only severe degrees of malforma-

tion have been recognized before complications occurred. Mild degrees of anomaly have been recognized predominantly at operation or by hystrogram and therefore have been considered most uncommon. Recently reported additional diagnostic criteria⁶ suggest that mild uterine malformations are quite common and in most cases are compatible with normal function.

Until recently only scattered reports considered obstetric performance in relation to specific anomalies. Pertinent to a proper interpretation of function is the important work of Jones⁹ in which classification was made according to physiologic capabilities (Table I) rather than anatomic description. Descriptive nomenclature although necessary to define specific malformations is an unreliable guide to predict physiologic performance.

It is the purpose of this paper to confirm certain aspects of prospective diagnosis and to report the incidence of anomalies so derived. The experience with pregnancy occurring in patients with these malformations seen at the North Carolina Baptist Hospital will be presented. In addition previous reports have been analyzed and summarized where possible according to the functional classification of Jones.

Diagnosis and incidence

In 1956, one of us (C. H. M.) began routine manual intrauterine exploration imme-

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diately following delivery. Initially this was done to exclude retained placental fragments and to exclude lesions such as submucosal leiomyomas. As the examiner's proficiency with this procedure increased, it was noted that an occasional uterus exhibited unusual contours. These consisted of a prominence of each cornual region, almost a pocket-like effect, in which the placenta was sometimes implanted and occasionally trapped requiring manual removal. Sometimes a definite midline septum could be palpated. At other times, a slight external midline depression was present in the fundus. More often, however, no definite defect was palpable but rather, one got the impression of focal abnormal contraction of the uterine musculature. This was unrelated to the administration of oxytocins. With more experience abnormal contours were noted in uteri formally palpated to be normal, and those with unusual contours were reaffirmed. Finally, at a repeat cesarean section for the second consecutive transverse lie, these contours were again felt, a slight midline intrauterine prominence was visualized, and a slight external midline fundal depression was noted. This was classified as an arcuate uterus. After involution, a hys-

terogram of this uterus showed a slight fundal depression although the film was read as "normal uterus." In Fig. 1, this hystero-gram is shown with that from a normal uterus. It should be obvious that subtle alterations of hystero-graphic contours are quite significant but rather easily overlooked.

In 1958, Hay,⁶ reported a series of 65 cases of minor degrees of uterine abnormalities diagnosed either prenatally or on intrauterine exploration. The diagnoses were all confirmed by hystero-graphy. In addition to more obvious prenatal criteria such as notching or asymmetry of the fundus, and abnormal fetal lies late in pregnancy, Hay noted other prenatal criteria, chief of which were abnormalities of fetal attitude. Consistent in all these instances was the phenomenon of "bilateral pocketing" noted on intrauterine exploration after delivery.

"The operator has the impression that the cornua of the uterus take the form of small pouches into which the exploring fingers or hand can be inserted. It is best appreciated by running the fingers up along the lateral border of the uterus and when the pocket is reached the hand appears to diverge laterally from the straight line.

Table I

<i>Functional classification (after Jones)</i>		<i>Descriptive equivalent</i>
I. The relatively good obstetric uterus with a relatively good cervix		Uterus arcuatus Uterus subseptus Uterus septus
A. Single uterus:	Septate cervix Septate or double vagina	
B. Septate uterus:	Single or septate cervix Single, septate or double vagina	
II. The poor obstetric uterus, with a relatively good cervix		Uterus bicornis unicollis
Bicornuate uterus:	Single or septate cervix Single, septate, or double vagina	
III. The relatively good uterus, with a poor obstetric cervix		Uterus bicollis
A. Single uterus:	Double cervix Single, septate, or double vagina	
B. Septate uterus:	Double cervix Single, septate or double vagina	
IV. The hemiuterus: A poor obstetric uterus with a poor cervix		Uterus didelphys Uterus unicornis
A. Double uterus and double cervix:	Single, septate, or double vagina	
B. Unilateral maturation of uterus and cervix		
V. Simple longitudinal (sagittal) vaginal septum		Same
VI. Transverse vaginal septum		Same

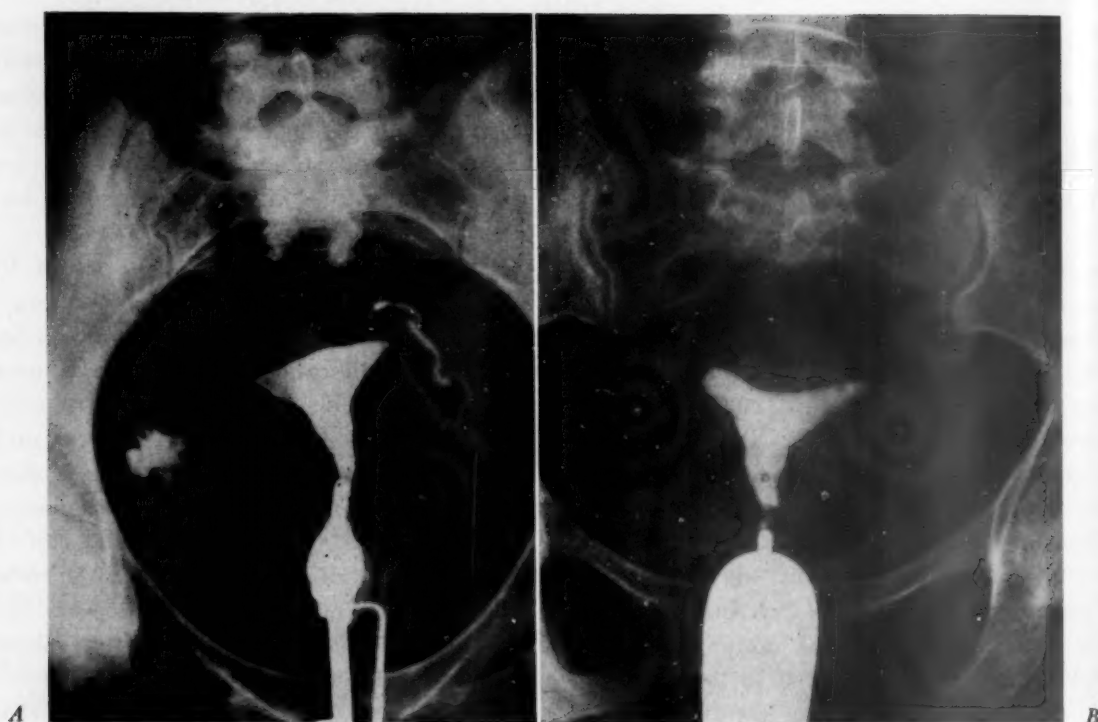


Fig. 1. Hysterothelms of normal uterus (A) and proved arcuate uterus (B).

Sometimes a pocket appears only when steady pressure is applied in the region of the cornu. Occasionally, as with the more marked types of uterine anomaly, a well defined ridge can be palpated at the fundus midway between the two pockets. When the muscle tissue surrounding the entrance to the pocket is in spasm, a sphincter-like opening to the pocket is appreciated."⁶

Of all the diagnostic criteria observed, Hay considered the finding of bilateral pocketing in uteri after delivery diagnostic of uterine anomaly. Our own experience confirms this impression.

Table II. Distribution of anomalies according to functional classification (NCBH series)

Group	No. patients	No. pregnancies
I	23	56
II	25	55
III	3	9
IV	11	22
V	0	0
VI	2	5

From Jan. 1, 1956, to Dec. 31, 1959, 661 intrauterine explorations have been performed and 22 anomalous uteri diagnosed by the criterion of cornual pocketing. These include 14 arcuate or subseptate uteri and eight bicornuate uteri. This is an incidence of 1:30 (3.3 per cent). Except for the more obvious signs of uterine abnormality, no attempt has been made to evaluate Hay's prenatal diagnostic criteria. (The reader is referred to Hay's article for a more detailed account of these criteria.)

Material

Since 1947, 77 women with anomalies of the reproductive tract have been observed at the North Carolina Baptist Hospital (NCBH). These include the previously mentioned 22 cases. Sixty-four patients conceived 147 times. Forty-four pregnancies were followed elsewhere. No attempt has been made to obtain a hospital incidence.

These anomalies have been grouped according to the classification of Jones (Table II). The high incidence of Group I lesions

reflects more recent diagnosis by intrauterine exploration. Twenty-two of the 23 cases in this group were diagnosed in the last 4 of our 13 year experience. No instance of an isolated longitudinal vaginal septum has been observed.

Results

Group I. The relatively good obstetric uterus with a relatively good cervix. Twenty-three patients conceived 56 times. With one exception, the performance of this group was quite comparable to normal (Table III). Breech and transverse presentation occurred in 4.1 per cent and 8.1 per cent, respectively. The inordinately high incidence of transverse lie accounted for 50 per cent of the cesarean sections. Primary and repeat cesarean sections were performed for breech presentation associated with relative disproportion and for uterine inertia. One perinatal death occurred in a patient with a transverse lie and placenta previa. The second death resulted from intracranial hemorrhage following a normal controlled spontaneous delivery. Prematurity was limited to one infant weighing 5 pounds, 5 ounces. Marked irregularity of fetal heart tones as described by Falls² was not observed.

Group II. The poor obstetric uterus with a relatively good cervix. This group comprised 25 patients and 55 pregnancies. Obstetric performance was the poorest of all the groups. In addition to the high abortion rate, abnormalities of presentation and premature emptying of the uterus were rampant (Table III). "Immaturity and pre-

maturity" accounted for 6 of the 7 viable fetal losses. The seventh death occurred in-trapartum at term. This patient exhibited profound primary uterine inertia, responsive only to high dosage of Pitocin stimulation. Irregularity of the fetal heart tones was present and cesarean section might have saved the infant.

The absence of cesarean sections in this group represents, in part, distribution error. One transverse lie converted spontaneously to a breech presentation in labor. One version and extraction from a transverse lie was performed because of prematurity. The infant, weighing 3 pounds, 13 ounces, survived. The second version from a transverse lie at term resulted in a viable but hemiparetic infant. Thus in Group II, more liberal use of cesarean section may have reduced fetal morbidity or mortality in only two instances.

Group III. The relatively good uterus with a poor obstetric cervix. Only 3 patients with isolated uterus bicornis were seen (Table III). All 8 pregnancies were terminated by cesarean section. Trial of labor was considered in only one patient. Breech presentation, myomata uteri, and a pelvis of borderline dimensions were the basis for abdominal delivery.

Too few patients were encountered in this group to permit any definite conclusions. However, our experience with the double cervix of the uterus didelphys suggests that vaginal delivery is not only possible but probable.

Group IV. The hemiuterus—a poor obstetric uterus with a poor obstetric cervix.

Table III. Obstetric performance (NCBH series)

Group	Abortion (%)	Breech (%)	Transverse (%)	Section (%)	Version (%)	Pre-maturity (%)	Viable fetal loss (%)	Gross fetal loss (%)
I (23/56)*	12.5	4.1	8.1	16.3	0.0	2.0	4.1	16.1
II (25/55)	29.1	7.7	7.7	0.0	5.1	38.5	17.9	41.8
III (3/9)	11.1	25.0	0.0	100.0	0.0	0.0	0.0	11.1
IV (11/22)	36.4	14.3	0.0	0.0	0.0	0.0	0.0	36.4
V (None)	—	—	—	—	—	—	—	—
VI (2/5)	20.0	0.0	0.0	0.0	0.0	0.0	0.0	20.0

*Figures in parentheses throughout indicate number of patients with number of pregnancies.

Table IV. Comparison of NCBH series and Jones results

	Group I		Group II		Group IV	
	NCBH (23/56) (%)	Jones (11/27) (%)	NCBH (25/55) (%)	Jones (64/169) (%)	NCBH (11/22) (%)	Jones (16/37) (%)
Abortion	12.5	22.2	29.1	33.8	36.4	32.4
Breech and transverse	12.2	28.6	15.4	20.5	14.3	40.0
Cesarean section	16.3	9.6	0.0*	20.5	0.0	68.0
Prematurity†	0.0	4.8	33.3	14.3	0.0	34.6
Viable fetal loss	4.1	0.0	17.9	9.7	0.0	19.2
Gross fetal loss	16.1	22.2	41.8	40.2	36.4	46.0

*5.1 per cent version and extraction.

†Below 5 pounds.

Table V. Obstetric performance—cumulative results—all groups

	Abortion (%)	Breech (%)	Trans- verse (%)	Section (%)	Version (%)	Prema- turity (%)	Viable fetal loss (%)	Gross fetal loss (%)
Miller ¹¹ * (32/67)	28.4	—	—	4.2	6.2	14.6	—	—
Falls ² (15/15)	—	6.7	0.0	26.7	13.3	13.3	13.3	—
Smith ¹⁴ (35/39)	12.8	44.2	17.6	14.7	0.0	—	14.7	25.6
Falls ³ † (155/155)	—	11.2	3.9	13.5	0.0	11.6	12.2	—
Schaufler ¹³ (11/32)	53.0	37.5	0.0	—	0.0	—	—	—
Taylor ¹⁵ (6/9)	11.1	12.5	0.0	12.5	0.0	0.0	0.0	11.1
Jarcho ⁸ (9/19)	36.8	0.0	16.7	33.3	8.3	16.7	16.7	47.4
Way ^{16, 17} (36/77)	14.3	12.1	24.2	15.2	10.6	24.2	28.8	38.9
Hunter ⁷ (17/42)	16.6	20.0	2.9	8.6	0.0	20.0	28.6	40.5
Fenton and Singh ⁴ (62/146)	26.0	14.8	2.8	28.7	0.0	22.2	18.5	39.7
Baker et al. ¹ (9/20)	35.0	23.1	0.0	15.4	0.0	23.1	15.4	45.0
Philpott and Ross ¹² (41/56)	28.6	10.0	7.5	15.0	0.0	17.5	5.0	32.2
Lash and Lash ¹⁰ (21/65)	26.2	27.1	0.0	20.8	0.0	16.6	—	—
Jones ⁹ (123/298)	27.2	22.8	—	29.0	0.0	13.2‡	9.1	33.9
Hay ⁶ (65/103)	14.6	13.6	4.5	14.8	0.0	—	5.7	19.4
NCBH series (64/147)	22.4	7.9	6.1	14.0	1.8	14.0	7.9	28.6
Total (701/1,290)	24.2	14.8	6.4	18.5	1.6	16.0	12.9	35.2

*Uterus didelphys only.

†Uterus arcuatus only.

‡Under 5 pounds.

Table VI. Obstetric performance—cumulative results—Group I

	Abortion (%)	Breech (%)	Trans- verse (%)	Section (%)	Version (%)	Prema- turity (%)	Viable fetal loss (%)	Gross fetal loss (%)
Falls (15/15)	—	6.7	0.0	26.7	13.3	13.3	13.3	—
Falls (155/155)	—	11.2	3.9	13.5	3.9	11.6	12.2	—
Jarcho (1/1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Way (5/10)	20.0	0.0	75.0	25.0	50.0	25.0	37.5	50.0
Hunter (2/8)	12.5	14.3	0.0	0.0	0.0	0.0	14.3	25.0
Fenton and Singh (12/35)	28.6	4.0	4.0	32.0	0.0	—	—	—
Lash and Lash (5/21)	33.3	35.4	0.0	7.1	0.0	0.0	—	—
Jones (11/27)	22.2	28.6	—	9.6	0.0	4.8	0.0	22.2
NCBH series (23/56)	12.5	4.1	8.1	16.3	0.0	2.0	4.1	16.1
Total (229/328)	20.9	9.9	6.2	15.6	4.1	8.9	10.5	21.6

Eleven patients in this group were delivered of 14 term infants with surprisingly little difficulty (Table III). Neither uterine inertia nor cervical dystocia occurred. Six infants weighed over 6 pounds, 8 ounces, and one infant weighing 7 pounds, 5 ounces was delivered precipitously. Usually the vaginal septum was displaced with ease. Incision was required in only one case. Frequently the septum was torn by stretching but it rarely required a suture. Gross fetal loss was confined to 8 spontaneous abortions. Although the abortion rate was quite high, premature emptying of the uterus after 20 weeks did not occur. Malpresentation was limited to 2 breech presentations.

Group V. Longitudinal vaginal septum.
No cases diagnosed.

Group VI. Transverse vaginal septum.
Two patients with isolated transverse vaginal septa presented as infertility problems. In each, excision of the septum eliminated the problem after which normal reproductive function occurred.

Comment

1. Anomalies of the uterus. To date, clinical experience has been our only measure of the obstetric capabilities of uterine anomalies. However, a knowledge of embryologic malformation alone enables one to predict areas of functional inadequacy. We must consider the effects of abnormal vascularization, particularly of developmental remnants, and the effects of physiologic as well as morphologic differences of the myometrium and cervix. Spontaneous abortion, adherent placenta, premature separation of the placenta, and placenta previa conceivably may result from circulatory insufficiency. Deviations from the normal uterine ovoid predispose to malpresentation. Transverse lie may occur when contours are irregular (arcuate, subseptate, or bicornuate uterus). Breech presentation often is associated with regular but altered contours (uterus bicolis, didelphys, or unicornis). Premature labor, uterine inertia, retained placenta, and malpresentation may be due to aberrations of

myometrial mass distribution and tonus. The severity of these tendencies should vary with the degree of abnormal development.

If one excludes placenta previa and premature separation of the placenta, the above logic is confirmed by our clinical experience. Uterine inertia occurred in only 2 cases, but in each it was profound. From our data, we could not calculate the incidence of retained placenta requiring manual removal but in almost every series of cases reported it is increased. In Groups I, II, and IV, where sufficient material was present, our results have been compared with those of Jones.⁹ They are quite similar (Table IV). In Group I, the major complication was malpresentation. Premature labor and malpresentation are the problems in Group II. Only in Group IV, the hemiuterus, do results conflict. Breech presentation is increased in both series, but in our experience gestational capacity, the forces of labor, and the ability of the cervix to dilate adequately were apparently normal. For uterus didelphys and uterus unicornis, Jones coined the terms "hemiuterus" and "hemicervix" since pregnancy is literally in half a uterus and delivery is through half a cervix. While it may be true that anatomically each hemiuterus has half or less than half the normal tissue mass, we do not believe that potential functional adequacy is so reduced since one cannot foresee the degree of muscle fiber hypertrophy or the absolute increase in muscle fibers that may occur in pregnancy. However, since such wide discrepancies in obstetric performance in small series may be explained by chance selection, the literature was reviewed and, where possible, results were tabulated according to the functional classification.

In Table V, specific complications of pregnancy are tabulated without respect to the type of anomaly involved. This represents experience with 1,290 pregnancies occurring in 701 patients. These results serve to re-emphasize two points: (1) the anomalous uterus is associated with an over-all increased incidence of complications of pregnancy; (2) evaluation of cumulative re-

Table VII. Obstetric performance—cumulative results—Group II

	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prema-turity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
Taylor (2/3)	33.3	0.0	0.0	0.0	0.0	0.0	0.0	33.3
Jarcho (3/8)	0.0	0.0	12.5	25.0	12.5	12.5	12.5	12.5
Way (31/67)	13.4	13.8	17.2	13.8	5.2	24.2	27.6	37.4
Hunter (7/13)	15.4	27.3	9.1	18.2	0.0	36.4	54.5	61.6
Fenton and Singh (14/37)	35.2	8.3	4.2	25.0	0.0	—	—	—
Baker et al. (6/16)	37.5	10.0	0.0	0.0	0.0	30.0	20.0	50.0
Lash and Lash (7/12)	8.5	8.2	0.0	54.5	0.0	8.2	—	—
Jones (64/169)	33.8	20.5	20.5	0.0	0.0	14.3	9.7	40.2
NCBH series (25/55)	29.1	7.7	7.7	0.0	5.1	38.5	17.9	41.8
Total (159/380)	27.6	11.7	9.8	17.1	2.2	21.9	17.9	40.5

Table VIII. Obstetric performance—cumulative results—Group III

	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prema-turity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
Hunter (1/4)	50.0	0.0	0.0	0.0	0.0	50.0	50.0	75.0
Jones (12/24)	20.0	40.0	65.0	0.0	0.0	10.0	0.0	20.0
NCBH series (3/9)	11.1	25.0	0.0	100.0	0.0	0.0	0.0	11.1
Total (16/38)	21.1	20.0	0.0	70.0	0.0	10.0	3.3	23.7

Table IX. Obstetric performance—cumulative results—Group IV

	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prema-turity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
Miller (32/67)	28.4	—	—	4.2	0.0	14.6	—	—
Schauffler (11/32)	53.0	37.5	0.0	—	0.0	—	—	—
Taylor (4/6)	0.0	16.6	0.0	16.6	0.0	0.0	0.0	0.0
Jarcho (5/10)	70.0	0.0	33.3	66.6	0.0	33.3	33.3	80.0
Hunter (7/17)	11.8	21.4	0.0	7.1	0.0	14.3	14.3	23.5
Fenton and Singh (22/54)	27.8	23.1	2.6	20.5	0.0	—	—	—
Baker et al. (3/4)	25.0	66.6	0.0	66.6	0.0	0.0	0.0	25.0
Lash and Lash (9/32)	28.1	26.1	0.0	13.0	0.0	26.1	—	—
Jones (16/37)	32.4	40.0	68.0	0.0	0.0	34.6	19.2	46.0
NCBH series (11/22)	36.4	14.3	0.0	0.0	0.0	0.0	0.0	36.4
Total (120/281)	32.0	23.1	1.7	20.6	0.0	18.4	10.4	39.6

Table X. Obstetric performance—cumulative results—Group V

	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prema-turity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
Fenton and Singh (9/12)	0.0	33.3	0.0	8.3	0.0	—	—	—
Jones (15/29)	3.4	10.7	0.0	0.0	0.0	10.7	14.3	17.2
Total (24/41)	2.4	33.3	0.0	2.5	0.0	10.7	14.3	17.2

Table XI. Obstetric performance—cumulative results—Group V

	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prematurity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
Fenton and Singh (5/8)	0.0	0.0	0.0	100.0	0.0	—	—	—
Jones (5/11)	0.0	0.0	0.0	45.5	0.0	9.1	0.0	0.0
NCBH series (2/5)	20.0	0.0	0.0	0.0	0.0	0.0	0.0	20.0
Total (12/24)	4.2	0.0	0.0	56.5	0.0	6.7	0.0	6.2

Table XII. Obstetric performance—cumulative results—groups compared

<i>Group</i>	<i>Abortion</i> (%)	<i>Breech</i> (%)	<i>Trans-verse</i> (%)	<i>Section</i> (%)	<i>Version</i> (%)	<i>Prematurity</i> (%)	<i>Viable fetal loss</i> (%)	<i>Gross fetal loss</i> (%)
I (229/328)	20.9	9.9	6.2	15.6	4.1	8.9	10.5	21.6
II (159/380)	27.6	11.7	9.8	17.1	2.2	21.9	17.9	40.5
III (16/38)	21.1	20.0	0.0	70.0	0.0	10.0	3.3	23.7
IV (120/281)	32.0	23.1	1.7	20.6	0.0	18.4	10.4	39.6
V (24/41)	2.4	33.3	0.0	2.5	0.0	10.7	14.3	17.2
VI (12/24)	4.2	0.0	0.0	56.5	0.0	6.7	0.0	6.2
All groups (701/1,290)	24.2	14.8	6.4	18.5	1.6	16.0	12.9	35.2

sults without respect to the specific anomaly fails to give an adequate picture of individual pregnancy performance. Tables VI to XI summarize results in the various anomaly groups, and Table XII compares these groups. Analysis of these statistics corroborates the aforementioned conclusions. However, it would appear from the high cesarean section and prematurity rates that over-all experience with the hemiuterus has been poor. While we are at a loss to explain absence of prematurity in this group, it is probable that our confidence in the abilities of the hemiuterus is responsible for the absence of cesarean sections.

One major criticism of the above results is that the incidence of complications is weighted by retrospective diagnosis. Therefore pregnancy results in our 22 cases, diagnosed without regard to complications, are presented in Table XIII. Although the number of cases is small, the results again confirm the previous conclusions that malpresentation and premature delivery are the principal complications in Groups I and II.

2. *Anomalies of the vagina.* The isolated

vaginal septum is probably the rarest of reproductive tract anomalies. Most often, it is the initial clue to discovery of additional malformations. Vaginal atresia, of which a transverse septum is only a focal manifestation, is commonly associated with agenesis of all organs of Müllerian origin. When it is found alone, the developmental defect occurred after fusion of the paired Müllerian ducts. Therefore, one would expect a normal uterus and functional inadequacy only at the vaginal level. Extreme degrees of

Table XIII. Obstetric performance—present series

	<i>Group I</i> (14/33) (%)	<i>Group II</i> (8/15) (%)
Abortion	12.1	13.3
Breech	0.0	15.4
Transverse	6.9	7.7
Cesarean section	6.9	0.0
Version	0.0	0.0
Prematurity	3.4	23.1
Viable fetal loss	0.0	15.4
Gross fetal loss	12.1	26.7

atresia probably explain the high incidence of soft tissue dystocia reported with this anomaly. On the other hand, a persistent longitudinal vaginal septum results from fusion defect. Similar defects at the cervical or corporeal level would be expected. An increased incidence of abnormal fetal presentations is reported with longitudinal septa but not transverse ones (Table XII). These findings support the contention that minor degrees of corporeal anomaly were present but were overlooked.

Summary and conclusions

Six hundred and sixty-one manual explorations of the uterine cavity immediately after delivery have been performed. Using the criterion of abnormal intrauterine contours, 22 uterine anomalies have been recognized. This is an incidence of 3.3 per cent. We believe that the presence of "cornual pocketing" at this examination is a reliable indication of minor degrees of uterine anomaly.

Seventy-seven women with anomalies of the reproductive tract have been treated at the North Carolina Baptist Hospital. In 64 patients, 147 pregnancies occurred. The obstetric performance in these pregnancies has been analyzed according to the functional classification of reproductive anomalies as suggested by Jones.

Seven hundred and one patients with 1,290 pregnancies from the literature, including the present series, have been similarly analyzed.

From these comprehensive statistics and our own results, we believe that the following conclusions are valid:

1. With specific exceptions, the physiologic capabilities of the anomalous uterus

are closer to normal than have been previously recognized. Diagnosis of these embryologic defects before complications arise will undoubtedly improve performance statistics.

2. Uterine anomalies are associated with an over-all increased abortion rate.

3. If reproductive anomalies are classified according to physiologic capabilities, the following obstetric inadequacies are most frequent:

Group I. Malpresentation, especially transverse lie.

Group II. Malpresentation, especially transverse lie; premature delivery.

Group III. Breech presentation; probably cervical dystocia.

Group IV. Breech presentation; probably premature delivery and cervical dystocia.

Group V. In the rare instance of a truly isolated longitudinal vaginal septum, no inadequacies should be expected.

Group VI. Soft tissue dystocia proportional to the degree of vaginal atresia.

Pregnancy and labor in a patient with anomalous reproductive organs should be managed no differently from pregnancy in the normal woman. Classification of anomalies according to their potential physiologic capabilities permits the physician an awareness of the more common problems that may arise. Although specific inadequacies may be anticipated, operative intervention should be invoked only when complications arise.

Too many women with "too many" uteri have been subjected to unnecessary operative procedures. It is hoped that future reports of uterine anomalies prospectively diagnosed and functionally classified will further clarify our thinking.

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Normal, living twins in uterus didelphys with 38 day interval between deliveries

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A PROLONGED time interval between the deliveries of living twin infants is extremely rare. Recently Drucker and associates¹ reported a 65 day interval between birth of twins and quoted Eastman as saying that this occurrence is usually limited to women with a pregnancy in each horn of a uterus didelphys.

Cope and Sharp,² in a review of the literature, found there were 400 published cases of uterus didelphys with associated pregnancy. Dorgan and Clarke,³ reviewing the literature, found only 3 authenticated cases of uterus didelphys with pregnancy in each uterine cavity resulting in delivery of viable infants.

This report presents a patient with twin pregnancy in a uterus didelphys who was delivered of living infants 38 days apart.

A 16-year-old Negro girl, gravida i, para 0, whose last menstrual period was March 15, 1959, and whose estimated date of confinement was Dec. 20, 1959, gave a history of spotting at 4 and 8 weeks. She was seen on one occasion prior to delivery. She never returned for prenatal examinations but eventually presented herself at Phillips Memorial Hospital on Nov. 21, 1959 (36 weeks), in time for delivery 5 minutes later at 10:05 P.M. A viable 2,130 gram female infant, who breathed and cried immediately, was delivered spontaneously from a left occipito-anterior position. The placenta was expelled intact. Superficial mucosal lacerations did not require repair. Blood loss was minimal.

Vaginal examination revealed a completely intact vaginal septum which extended from the introitus separating the 2 cervices and forming 2 vaginas. This was diagnosed as uterus didelphys with a septate vagina. An undelivered viable fetus with normal heart rate was present with a cephalic presentation in the right uterine cavity. The fundal height of the right horn measured (tape measure) 36 cm. above the symphysis. The left uterine horn from which delivery had been effected remained well contracted without benefit of oxytocics. There was no postpartum hemorrhage and there was no attempt toward contraction of the pregnant uterine horn. The cervix remained long and closed and membranes were intact.

Findings on general physical examination were normal except for the uterus didelphys and the remaining fetus in utero. An x-ray examination of the abdomen at this time revealed a single fetus in a vertex presentation on the maternal right side.

The hematologic study revealed a 29 per cent hematocrit, 8.2 Gm. of hemoglobin, and a 7,500 white blood count with normal differential. The patient was given 500 c.c. of whole blood on Nov. 26, 1959.

During the hospital stay she remained afebrile. Since no complications developed, conservative therapy was decided upon and she was discharged on Nov. 27, 1959. Because of lack of cooperation on the part of the patient, periodic examinations were performed at her home.

She was readmitted complaining of abdominal pain on Dec. 29, 1959 (5½ weeks after first delivery), at 11:10 P.M. Vaginal examination revealed the fetus to be in a vertex presentation, a

minus-1 station, 6 cm. cervical dilatation, and intact membranes. Fetal heart tones were normal. At 11:53 P.M. a 2,970 gram viable female infant who breathed and cried immediately was delivered spontaneously. The placenta was delivered intact. Blood loss was approximately 100 c.c. The postpartum course was uneventful and the patient was discharged on Jan. 1, 1960. An attempt at breast feeding was unsuccessful and each infant was eventually bottle fed. No breast-drying medication was given. The coloring and anatomic features of the infants are similar so that one sister closely resembles the other. One twin's blood group is type A, Rh positive, and the other's is type O, Rh positive. The mother's blood type is A, Rh positive. The father's blood grouping is not available.

Comment

Most authorities feel that each case of uterus didelphys associated with pregnancy should be individualized with regard to management.

This patient did not develop any complications during the 6 day hospitalization after delivery of the first twin. Interference in a pregnancy that is progressing satisfactorily may be construed as meddling and possibly result in unforeseen complications. A knowledge of complications and what steps to take is necessary and should determine whether conservative therapy (expectancy), induction, or cesarean section is indicated. Because the patient had been delivered of the first twin without incident, it was decided to handle the remaining twin in the same manner.

The first infant weighed 4 pounds, 7 ounces (2,130 grams), and was in the premature category by weight. The second infant, delivered 38 days later, weighed 6 pounds, 3 ounces (2,970 grams). This is a difference of 1 pound, 12 ounces (840 grams) and is apparently in part due to the fact that the second infant remained in utero 38 days longer. The birth weight is not always an accurate measurement of whether an infant is premature or term. Greenhill⁴ stated that a child of 9 months' gestation may weigh 3.5 pounds while one of 8 months may weigh 8.5 pounds. An example of this

weight differential is offered in a case of full-term monoamniotic twins (thus known to be of the same gestational age) in which both infants were normal and survived.⁵ One twin weighed 4 pounds, 11 ounces and the other weighed 6 pounds, 1 ounce. This would illustrate that there are other factors which affect an infant's development and weight besides length of pregnancy. Uterus didelphys is an abnormal situation in the human. Variations exist in the uterine musculature of the two uterine horns. Lack of vascularity of the implantation site or placental insufficiency may be a contributing factor in weight variation.

The question of the definition of superfetation being applied to uterus didelphys needs to be clarified. Superfetation (in its simplest definition) is fertilization of two ova derived from different ovulations (different menstrual cycles). Another related facet to this picture is superfecundation which is defined as two ova being fertilized within a short time interval (in the same menstrual cycle), but not at the same coitus. This is recognized in lower animals.⁶

Whether or not superfetation can occur in uterus didelphys may be evidenced by hematologic studies (ABO; Rh-Hr; M,N; S-s; Kell) as in cases of paternity litigation. Various sources differ in their definition of superfetation. It has never been proved in the human and is not supposed to occur since pregnancy theoretically inhibits ovulation. An element of confusion arises in considering a further definition of superfetation as "the nesting of a second fetus in a uterus already occupied by one in the process of development." This would follow the general definition of requiring another ovulatory cycle to occur, but would seem to indicate that the definition could be fulfilled only in a single uterine cavity. Another author states that superfetation is out of the question at the end of the third month of pregnancy when fusion of the decidua vera and decidua reflexa occurs. He goes on to say it could occur in uterus duplex (uterus didelphys). Actually it could occur in uterus didelphys even in the last trimester of pregnancy as

long as ovulation occurs and the nonpregnant uterine cavity is not obliterated. Present-day multiple pregnancies from a single uterus are generally recognized and delivery usually accomplished without a time lapse of days or weeks. A source with a potentially great time lapse between deliveries is available for consideration as future cases of twins in uterus didelphys are reported.

If a situation arose where blood group studies irrefutably excluded paternity of one twin in single or double uterine pregnancies, a case of superfecundation will have been proved by hematologic studies. If a similar situation were to happen with a lapse of weeks between deliveries as in twin pregnancies from uterus didelphys in which there was hematologic evidence excluding paternity of one twin, the question of superfetation would arise. Statistically this is rare if not improbable; however, an awareness of its possible existence is necessary for recognition. Present advances in technology to assist in proving or disproving theories should be utilized. This concept with a review of some of the legal problems is very simply presented by Eastman.⁷

The exact cause or causes of the initiation of labor has not yet been answered. Uterus

didelphys, which is present as a normal occurrence in some animals is a source of material for research and investigation. Twin pregnancies in uterus didelphys in which labor does not occur simultaneously may be helpful in answering this question.

Summary

1. This is a case of uterus didelphys and double vagina with a pregnancy in each uterine cavity.

2. There was a lapse of 38 days between the two deliveries.

3. The labor and the delivery of each female infant was uneventful.

4. The weight of the first infant was 4 pounds, 7 ounces and the weight of the second infant was 6 pounds, 3 ounces.

5. Both sisters have developed normally and are in good health a year later.

6. The definition of superfetation and its relation to uterus didelphys requires clarification.

7. Cases of twin pregnancy in uterus didelphys (man or animal) are a good source for investigating the initiation of labor and to determine whether superfetation occurs in the human.

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GYNECOLOGY

Diagnosis and results of therapy of ovarian tunica fibrosa with cystic changes

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PREVIOUS communications^{1, 2} have described the criteria and indications for the use of intravenous estrogen in women who show ovulatory failure. It was reported that in those anovulatory patients in whom abnormalities of thyroid or adrenal function had been ruled out or corrected and in whom there was still adequate ovarian function to produce a proliferative phase endometrium, the administration of 20 mg. of conjugated estrogens, equine (Premarin) intravenously provided a diagnostic differential between the women who were capable of ovulating and those in whom some barrier to ovulation was postulated. Further experience with the diagnostic approach outlined in the earlier reports has extended and confirmed the original findings on the usefulness of intravenous estrogen as both a diagnostic and a therapeutic tool in patients with ovulatory failure.

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Those patients who did demonstrate an ovulatory response to the intravenous estrogens were investigated only as far as their fertility potential in response to such therapy. By virtue of a positive response, they demonstrated normal pituitary-ovarian interrelationships and thus were not considered to be candidates for laparotomy. Of this group of infertile positive responders in whom the average duration of infertility was 4 to 5 years, 13 of 18 became pregnant, with pregnancy occurring in direct time relationship to the induction of ovulation by this procedure.

This report will present some of the more recent data obtained in the category of patients classified as "negative responders" to intravenous estrogen. This is the most controversial group in that exploratory laparotomy with bilateral ovarian wedge resection has been recommended for these patients on the basis of their persistent failure of response to three or more trials at induction of ovulation with intravenous estrogen. Oftentimes the negative response is the only objective indication for operation in these anovulatory, infertile, but otherwise normal women. Trials of intravenous estrogen in

Table I

Case No.	Operation done	Clinical features					Menses after operation	Pregnancies after operation	Remarks
		Obesity	Hypertension	Hirsutism	Clitoral enlargement	Enlarged ovaries			
1*	Yes	+	0	±	0	±	Ovulatory	2	Spontaneous abortions (2)
2	Yes	0	0	0	0	0	Ovulatory	2	Ectopic pregnancies (2)
3	Yes	0	0	0	0	0	Ovulatory	0	
4*	Yes	0	0	+	0	0	Ovulatory	0	4 year history of secondary sterility before operation
5	Yes	0	0	0	0	0	Ovulatory	0	
6*	Yes	0	0	0	0	0	Anovulatory	0	Hypoplastic internal genitals
7	Yes	0	0	0	0	0	Ovulatory	1	
8	No	+	0	0	0	0	—	—	Lost to follow-up
9	Yes	+	0	+	0	0	Ovulatory	1	
10	Yes	0	0	0	0	0	Ovulatory	2	
11	Yes	+	0	±	0	0	Ovulatory	0	
12*	Yes	+	0	+	+	0	Anovulatory	0	Hypoplastic internal genitals
13	Yes	0	0	0	0	0	Ovulatory	1	
14	Yes	0	0	+	0	0	Ovulatory	0	
15*	Yes	0	0	0	0	0	Ovulatory	1	
16	Yes	0	0	0	+	±	Ovulatory	1	
17*	Yes	+	0	0	0	0	Anovulatory	—	
18	Yes	+	0	0	0	0	Ovulatory	0	
19	Yes	±†	0	±	±	0	?	?	Operated October, 1959
20	Yes	0	0	0	0	0	?	?	Operated October, 1959

*Case presented in some detail in text.

† = present to a mild or minimal degree.

the patient with clinically diagnosable Stein-Leventhal syndrome with large bilaterally palpable polycystic ovaries also failed to induce ovulation, as might be anticipated. Since these patients present no diagnostic problem from either physical or culdoscopic examinations, they are not the subject of this report. Without the classical physical findings of the Stein-Leventhal syndrome,³ however, many of these patients have gone unrecognized and many physicians have assumed that the negative response to intravenous estrogens represents a failure of the techniques rather than a failure of the patient and hence will have misinterpreted a diagnostic clue. Therein lies the controversy.

Several specific case histories and the results obtained to date at this institution in regard to the surgical pathology and subsequent fertility of such patients are pre-

sented in the hope of improving our understanding of the pathophysiology of ovulatory failure due to ovarian tunica fibrosa with cystic changes or the Stein-Leventhal syndrome.

Methods

It cannot be emphasized too strongly that no woman was subjected to a diagnostic test with intravenous estrogen without her first being shown to fulfill the following criteria: (1) normal thyroid function, (2) normal adrenal function, (3) adequate estrogenic secretion by the ovary to induce proliferative changes in the endometrium.

Thyroid function was judged not only by the usual clinical evaluation but also by serum protein-bound iodine or radioactive iodine uptake studies, serum cholesterol, and a 5 hour glucose tolerance test. Adrenal function was also evaluated not only by

clinical criteria but also by the determination of urinary 17-ketosteroids and/or pregnanetriol levels in a 24 hour specimen.

If abnormal thyroid and/or adrenal function was noted, by any of the aforementioned parameters of activity, appropriate steps were taken to correct this abnormality prior to the use of the intravenous estrogen.

Endometrial biopsies and/or basal body temperature charts plus a history of infertility unmasked the ovulatory failure in those patients with spontaneous menses from a proliferative endometrium. In women with amenorrhea of varying duration, the menstrual response to a standard dose of 100 mg. of progesterone in oil, intramuscularly, indicated the adequacy of endogenous estrogen production. Since progesterone cannot exert its effect upon an unprimed endometrium, the objective evidence of progesterone withdrawal bleeding occurring within 2 weeks of its administration implies that sufficient follicular phase activity of the ovary existed to induce adequate estrogen priming of the endometrium. This response to progesterone is a more direct measure of the physiologic effects of endogenous estrogen than other techniques such as vaginal smears or estrogen assays.

The 20 mg. of conjugated estrogens, equine, was administered intravenously no earlier than 14 days after the preceding menstrual period, either spontaneous or progesterone-induced, and even as late in the menstrual cycle as the sixty-fourth day.

It is important to state that the recommendation for surgical intervention was made only in those women *desiring fertility* who failed to respond to at least three attempts at induction of ovulation with the estrogen. Most of these women were also evaluated for objective evidence of tubal patency (tubal insufflation or hysterosalpingography) before ovarian wedge resection was recommended, and their husbands' semen also were checked. It is to be emphasized that bilateral ovarian wedge resection is not indicated in the unmarried woman until the time that she undertakes marriage

and desires fertility—unless impending complete ovarian failure threatens. Ovarian failure is manifested in these adults by decreased endogenous estrogenic secretion, as evidenced by an estrogen-deficient vaginal smear and by amenorrhea with a failure of menses to occur after a test dose of progesterone.

Thus, the group of patients in this report represents a highly selected group of (1) eumorphic, (2) euthyroid, (3) euadrenal, (4) persistently anovulatory, (5) married women with (6) a fertility problem.

Results and comment

The 20 patients in this series are only those women in whom the diagnosis of tunica fibrosa of the ovary was made solely on the basis of their persistent failure of

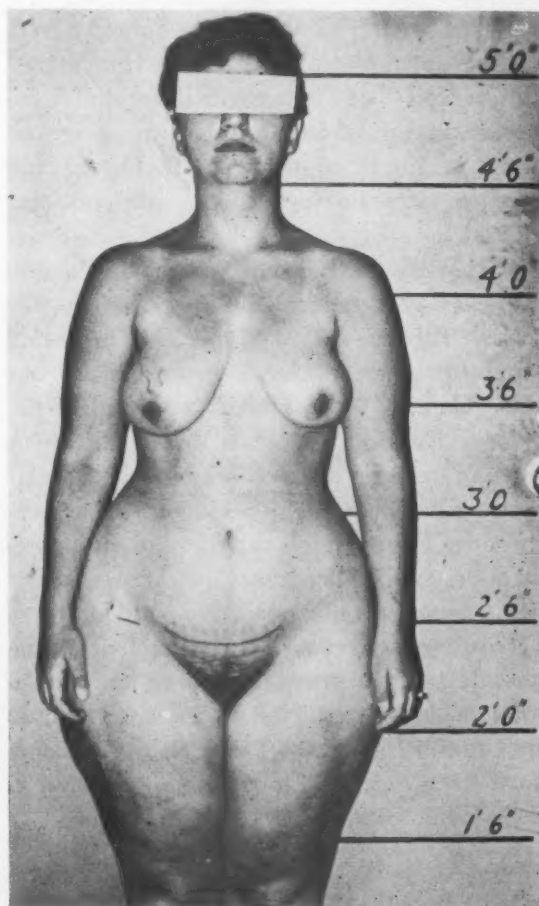


Fig. 1. Case 1, Patient J. K., after bilateral ovarian wedge resection.

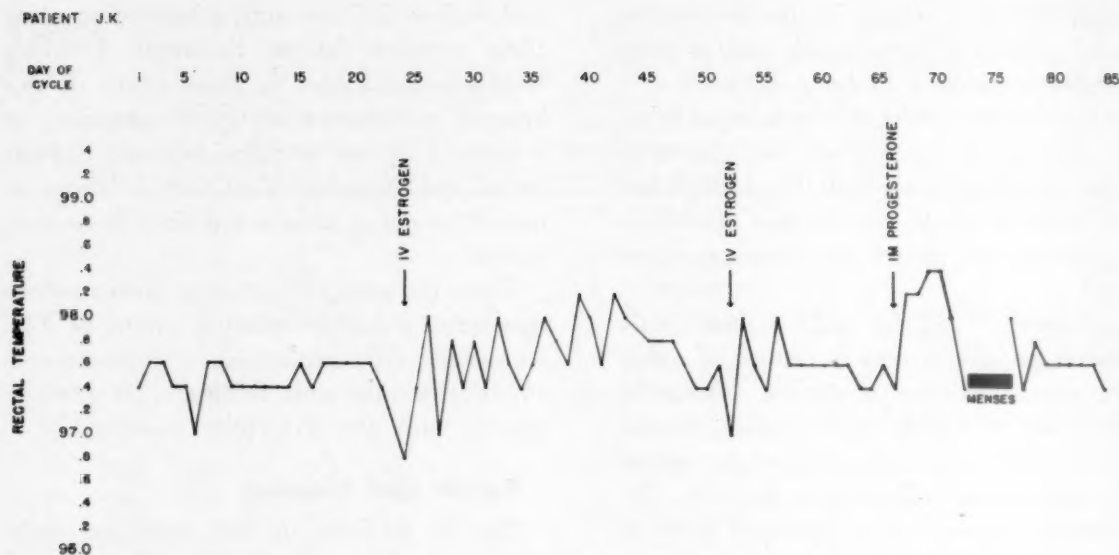


Fig. 2. Basal temperature chart showing failure of the induction of ovulation with each of two intravenous estrogen injections.

ovulation in response to intravenous estrogens after at least 3 trials. Patients who bore the classical physical stigmas (obesity, hirsutism, amenorrhea, and large palpable cystic ovaries) of the Stein-Leventhal syndrome, and in whom a presumptive diagnosis could be made on the basis of history and physical examination alone, are not included.

It is particularly gratifying that, of the 20 patients with normal-sized ovaries in this series (Table I), 19 or 95 per cent have had laparotomy up to this time, and in all but one (Case 17) the anticipated surgical pathology has been found: a thickened fibrous ovarian capsule with subcapsular follicular cysts, with or without evidence of hyperthecosis. Fourteen of the 19 patients operated on, or 74 per cent, are known to be ovulatory after the operation, and of these 14 ovulatory women 8 (57 per cent) have already become pregnant. There has been a total of 11 pregnancies in the latter group. In Cases 19 and 20 (Table I) the patients have been operated on only recently, and their ovulatory status is still in doubt.

Case 1. J. K. was a 21-year-old student nurse with a history of completely irregular menses since her menarche at age 14½ (Fig. 1). There

were long periods of amenorrhea unless menses were induced by progesterone, to which she responded well with controlled vaginal bleeding occurring usually within 4 to 6 days of this therapy. The patient had some tendency to obesity which varied with her dietary intake, but no acne or hirsutism. Physical examination was unremarkable except for moderate obesity (weight of 147 to 152 pounds), a slightly increased



Fig. 3. High-power view of microscopic section of the ovary resected in Case 1. The thickened fibrotic ovarian capsule can be seen running diagonally across the top of the section, with part of the lining of a subcapsular follicular cyst beneath.

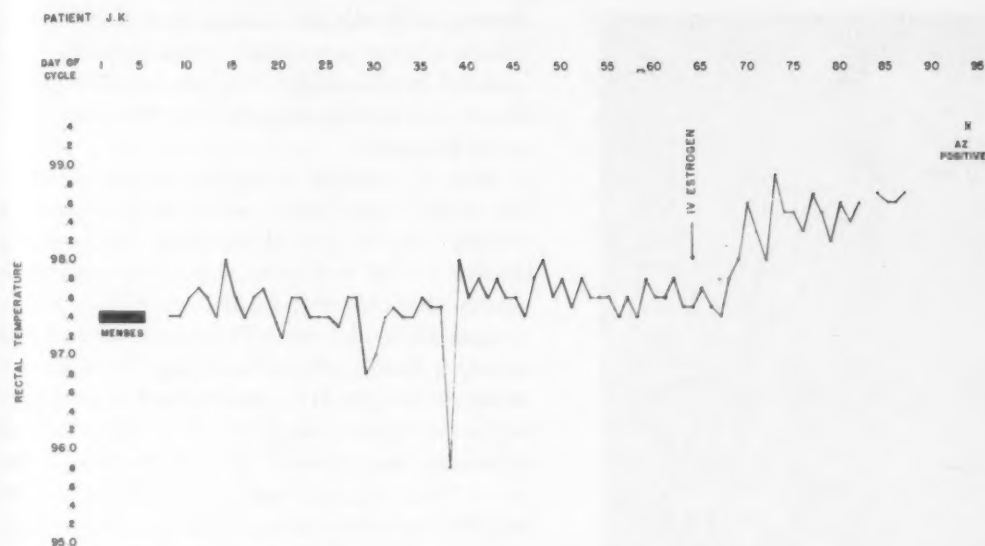


Fig. 4. Ovulatory response to intravenous estrogen in Patient J. K., occurring after ovarian wedge resection.

amount of dark lanugo facial hair, and minimal enlargement of the left ovary on pelvic examination. Laboratory studies revealed a protein-bound iodine (PBI) level of 7.3 mcg. per cent, 17-ketosteroids of 14.0 mg. per 24 hours (normal), normal serum cholesterol, and a normal glucose tolerance curve. The basal body temperature records were persistently anovulatory in character, showing a temperature rise only while the patient was on exogenous parenteral or oral progestational therapy. An attempt was made to induce ovulation by the injection of 20 mg. of conjugated estrogens, equine (Premarin) intravenously. She failed to ovulate after each of four such attempts and the basal body temperature chart, showing her negative response to two intravenous estrogen injections, may be seen in Fig. 2. In the interim, the patient married and in May, 1957, a bilateral ovarian wedge resection was performed. The operative findings confirmed the diagnosis of polycystic ovaries of normal size, with a thickened ovarian capsule. The microscopic section of the resected ovaries is seen in Fig. 3. Postoperatively, the patient had irregular, but ovulatory, menses occurring spontaneously in June, August, and October. When she was seen on Dec. 10, 1957, her last menstrual period had been Oct. 7 to 11, 1957, and her temperature chart was monophasic (Fig. 4). Once again, intravenous estrogen was given as 20 mg. of Premarin on the sixty-fourth day of the menstrual cycle and was followed by a classic postovulatory maintained rise in basal body tem-

perature. The blood Aschheim-Zondek test was positive on Jan. 9, 1958. Unfortunately, the patient had a spontaneous abortion shortly thereafter. A second pregnancy 6 months later also terminated in spontaneous abortion in the second month of gestation.

Comment. This case is of particular interest because it illustrates the negative ovulatory response to intravenous estrogen before operation, and the excellent positive ovulatory response to the same therapy given during a prolonged anovulatory phase, after bilateral ovarian wedge resection.

Case 4. W. G. was a 27-year-old woman who had her menarche at age 13 (Fig. 5). Menses were always irregular with periods occurring only every 3 to 6 months. She had been married for 2½ years and had had one pregnancy in December, 1954, which resulted in a 7 month gestation with a stillborn infant. Subsequent to this pregnancy, she developed secondary sterility of 2 years' duration and periods of amenorrhea of 6 months' duration. Her referring physician had placed her on cyclic substitution therapy with sex steroids to induce monthly menstrual flow. The rest of the patient's history was unremarkable. Physical examination revealed a well-developed woman 65 inches tall, weighing 125¾ pounds, with an increased amount of hirsutism of the face and abdomen, and a male escutcheon. The rest of the physical examination, including pelvic findings, was entirely normal. Laboratory studies revealed a PBI of 5.0 mcg. per cent, cholesterol

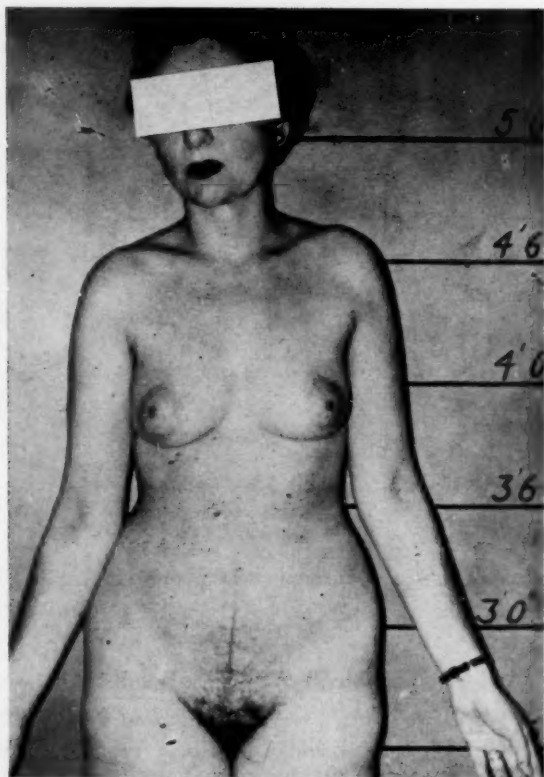


Fig. 5. Case 4, Patient W. G., a eumorphic woman who developed tunica fibrosa of the ovaries subsequent to a previous pregnancy.

level of 216 mg. per cent, normal glucose tolerance test, 17-ketosteroids of 9.1 mg. per 24 hours, and pregnanetriol level of 1.0 mg. per 24 hours. On the basis of normal results in the measures of thyroid and adrenal function and the patient's menstrual response within 2 weeks of the parenteral administration of progesterone in oil, it was decided to attempt to characterize further the ovulatory defect. An attempt to induce ovulation was made with intravenous estrogen given at appropriate times in the menstrual cycle, as previously discussed. The patient failed to ovulate after each of the three trials and a bilateral ovarian wedge resection was recommended. The operation was performed in August, 1957, at which time the presumptive diagnosis was confirmed. A microscopic section of a portion of the normal-sized ovary removed at operation is shown in Fig. 6. Postoperatively, menses have become ovulatory with biphasic basal temperature records, but the patient has not yet become pregnant.

Comment. Case 15 was similar in that the patient presented with secondary sterility, having previously been delivered of a stillborn infant.

Subsequently, she too became persistently anovulatory without any other endocrinopathy until bilateral ovarian wedge resection was performed. About 3 months postoperatively this patient became pregnant.

These 2 patients demonstrate that ovulatory failure due to polycystic ovaries with a thickened capsule may develop at *any* stage in the reproductive life of a woman and is not necessarily a congenital or menarchal defect.

Case 12. R. R. was a 25-year-old woman with a 3 year history of sterility (Fig. 7). Since her menarche at age 11½, menses had been irregular, occurring only every 2 to 3 months. She had previously had periods of amenorrhea lasting for as long as 1 to 2 years, and when first seen had not had a menstrual period in 3 years. There was no history of dysmenorrhea. In the 3 year period of amenorrhea, she had put on a great deal of weight. She had noted facial and sacral hirsutism since age 16, increasing in amount more recently, but there was also a family history of hirsutism. The rest of the history was unremarkable. Physical examination revealed a well-developed, obese woman, weighing 197½ pounds with blood pressure of 92/60 mm. Hg. There was an increased amount of coarse dark hair of the face, breasts, sacrum, and inner thighs. The breasts were well developed. There were some faintly purple striae over the right flank area. There was significant, moderate clitoral enlarge-

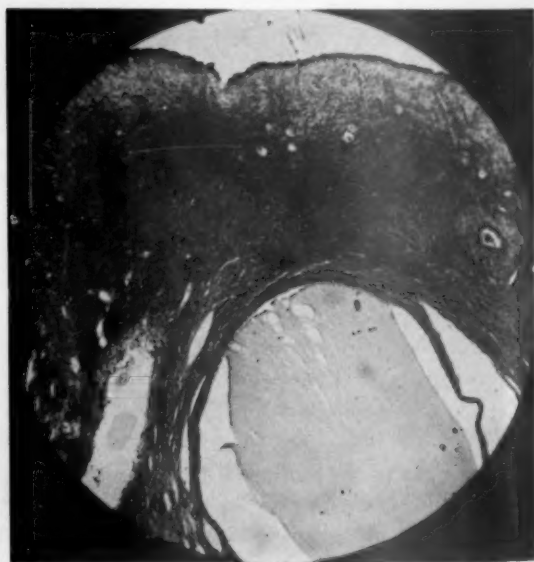


Fig. 6. Microscopic section of the resected ovary of Case 4. The thickened fibrotic capsule can be seen at the top of the field with part of a large subcapsular follicular cyst beneath.

ment. Pelvic examination was unsatisfactory because of the obesity, but there was no adnexal enlargement or tenderness. The rest of the findings were normal. The laboratory studies showed a PBI of 6.3 mcg. per cent, 17-ketosteroids of 10.8 mg. per 24 hours, 17-hydroxycorticoids of 4.2 mg. per 24 hours, cholesterol of 234 mg. per cent, and BMR of plus-2 per cent. The patient responded by having her first menstrual period in 3 years, 7 days after the intramuscular administration of 100 mg. of progesterone in oil. Twenty-one days after this induced catamenia, induction of ovulation was attempted by intravenous estrogen but was unsuccessful as were 2 later similar trials. The basal temperature record remained anovulatory throughout.

On the basis of the aforementioned findings, operation was recommended, and in March, 1958, the patient had a bilateral ovarian wedge resection. The operative findings were unusual in showing hypoplasia of the internal genitals, described by the surgeon (Dr. Gordon W. Douglas) as follows:

The uterus was quite small and hypoplastic in appearance, measuring perhaps 5 cm. in length. The round ligaments were difficult to identify and vestigial in character. Both Fallopian tubes were very thin and small in caliber, but elongated and swung upward in a vertical position, so that the fimbriated extremity lay at the pelvic brim. The ovarian ligaments on each side were similarly attenuated and elongated, each measuring 5 cm. in length. The ovaries themselves were globular, white, smooth, and on section revealed multiple small cysts. . . .

This patient had only one ovulatory menstrual period which occurred exactly 32 days after the operation, but since then she has reverted to anovulatory cycles, still with a persistently negative response to intravenous estrogens.

Comment. This case is presented because the one other patient (Case 6), who had identical findings of genital hypoplasia at operation, has also remained anovulatory after ovarian resection. It is interesting to speculate whether, in general, these operative findings may represent a poor prognostic sign as to ultimate ovulation and fertility in others with similar findings. Unfortunately, as far as is now known, there is no way of differentiating this group of patients preoperatively. Culdoscopy, even when done by the most skilled operators, has proved to be of little diagnostic aid in those patients with either normal or small ovaries.

Case 17. The third patient who remained



Fig. 7. Case 12, Patient R. R., who had tunica fibrosa of the ovaries, but who also had marked hypoplasia of the internal genitals, and remained anovulatory postoperatively.

anovulatory postoperatively deserves special mention. The diagnostic evaluation was identical to that already outlined and she showed a failure of ovulatory response to each of four injections of intravenous estrogens, administered at appropriate times in the menstrual cycles. Operation was performed, and the operative findings showed marked subacute pelvic inflammatory disease such that wedge resection of only one ovary was possible, and even on that side the tissues were fragmented. The surgeon's report stated that grossly the one ovary showed a smooth, white surface (which may also be seen in pelvic inflammatory disease) and although one area showed the typical fibrotic capsular thickening usually associated with the Stein-Leventhal syndrome, the linear alignment of primordial follicles was missing and there were no small cystic subcapsular follicles as are usually expected. Very little of the hilus of this subacutely inflamed ovary could be removed. The surgeon felt that in view of the moderately extensive pelvic inflammatory disease and the necessary inadequacy of the ovarian wedge resection which resulted from it, pregnancy was probably most unlikely in this case.

Comment. Despite the fact that the usual

typical pathology of tunica fibrosa with cystic changes was not found in Case 17, this case cannot be classified as an error in preoperative diagnosis for certainly the patient showed some of the pathologic features of this disease and was persistently anovulatory with the only hope for eventual fertility lying in whatever surgical correction could be accomplished.

Whether intravenous estrogen is given as therapy to induce ovulation in those women who are capable of ovulating, but who do so only irregularly, or whether it is used for diagnosis in clinically normal patients with a thickened ovarian capsule and persistent ovulatory failure, this procedure is recommended only after thyroid and adrenal gland function has been shown to be normal, as originally described.^{1, 2} It is only then that the procedure may be anticipated to have a high percentage of success and that negative ovulatory responses to the intravenous injection may be considered valid evidence for recommending ovarian wedge resection. Rigid adherence to such a diagnostic evaluation in the cases handled by us has resulted in no errors in the preoperative diagnosis, and no unnecessary operation has been done to date. Surgical treatment is reserved only for those women who present fertility problems or those in whom complete ovarian failure threatens.

Summary

Follow-up results are presented on a series of 20 patients who had essentially normal pelvic findings and normal thyroid and adrenal function, but who were anovulatory with problems of infertility. These patients all showed a persistent failure of response

to three or more attempts at induction of ovulation with 20 mg. of intravenous estrogen, equine, given 14 or more days after the preceding catamenia. It was this persistent failure of ovulation which prompted recommendations for ovarian wedge resection in all of these otherwise clinically normal, married, but infertile women. The preoperative diagnosis of tunica fibrosa of the ovaries with cystic changes has been confirmed grossly and by microscopic sections of the resected tissue in 18 of the 19 operated cases. In the seventeenth case, the ovarian surgical pathology was primarily that of subacute, marked pelvic inflammatory disease although there were also areas suggestive of a thickened fibrotic ovarian capsule. Only 2 of the other 18 patients who have had operations and who have been followed for a sufficient length of time have failed to ovulate postoperatively, and both of these cases were unusual in that the patient showed marked hypoplasia of the internal genitals, as contrasted with the other 16 cases where ovaries, uterus, and Fallopian tubes were normal in size. It is suggested that this condition accompanied by internal genital hypoplasia may represent a variant which bears a poor prognosis for eventual fertility. There has been as yet no satisfactory technique for preoperative differentiation of the two types of ovarian tunica fibrosa.

We gratefully acknowledge the supplies of intravenous conjugated estrogens, equine (Premarin) that were made available through the courtesy of Dr. John Jewell of the Ayerst Laboratories.

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A critique of the Stein-Leventhal syndrome

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THE purpose of this presentation is to attempt to clarify the present-day concept of the Stein-Leventhal syndrome. In 1935, Stein and Leventhal¹ first called attention to a syndrome which was characterized by the pathologic picture of large, pale, polycystic ovaries with thickened capsules which was commonly associated with menstrual dysfunction and sterility. Since that time, a rather large volume of literature devoted to the various aspects of this particular syndrome has accumulated.

Stein and Leventhal, in the initial phase of their investigation of this entity, were curious to ascertain whether biopsy of the ovaries would yield a clue to the etiology of the condition. They performed a bilateral ovarian wedge resection for the purpose of biopsy, and found that in a high percentage of their cases normal reproductive function was restored. Because of this unexpected end result, the bilateral ovarian wedge resection, intended only as a biopsy, was adopted as a therapeutic technique. They reported these studies.¹

Etiology

The etiology of this syndrome is obscure, and the theoretical proposals thus far presented in the literature leave much to be desired,¹⁻⁶ and none of these theories helps very much in explaining the successful results from wedge resection of the ovaries.

Incidence

The incidence of the typical syndrome is very low. Johansson,⁷ in a study of 370

thoroughly evaluated infertile women, found 5 instances (1.45 per cent). Leventhal and Cohen⁸ performed culdoscopy on 316 patients complaining of infertility and found typical polycystic ovaries in 9, or 2.8 per cent. Stein¹³ and Leventhal and Cohen⁸ have accumulated a total of 114 cases in 29 years at Michael Reese Hospital, thus, emphasizing the infrequency of this syndrome. In my own practice, I have found 10 cases of this syndrome in 611 patients with a primary complaint of infertility (1.6 per cent). All of these cases have been detected in the past 5 years. The findings and results of treatment of these 10 cases are recorded in Table I.

Clinical picture

It is important always to keep this syndrome in mind when one is dealing with any menstrual abnormality associated with infertility. Characteristically, menarche occurs at the usual time in these patients. The menses are relatively normal for a few years; then they become progressively infrequent and scant. These patients usually show the normal feminine body characteristics. If one accepts the definition of secondary amenorrhea as a nonappearance of bleeding for a year or longer, many more of these patients would be called oligomenorrheic rather than amenorrheic. The amenorrhea or oligomenorrhea is of variable duration but it usually persists until effective treatment is instituted. A few pregnancies have been reported in some patients prior to the development of the menstrual aberration and the diagnosis of this syndrome. One of our patients (Case 8) was delivered of a full-term pregnancy 14 months before the diagnosis was established by culdoscopy and wedge re-

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Table I. Summary of 10 patients with Stein-Leventhal syndrome out of total of 611 infertile women

Case	Age	Menstrual history	Hirsutism	Sterility	Obesity	Pre-operative culdoscopy	17-Keto-steroids	Size of polycystic ovaries	Menses after operation	Pregnancy after operation
1. C. V.	21	Oligomenorrhea Menses 6 to 10 weeks	No	Primary	No	No	No	Right, 4 times normal Left, normal	Normal	3 normal 1956, 1957, 1958
2. W. N.	23	Second amenorrhea No menses 6 years	No	Primary	No	Yes	No	Normal	Normal (an-ovulatory)	None
3. J. T.	27	Oligomenorrhea Menses 6 to 12 weeks	Mild	Primary	No	Yes	Normal	Normal	Normal	2 abortions (no fetus) 1 normal Nov., 1959
4. R. D.	22	Metrorrhagia Continuous 10 years	No	Primary	No	Attempt	No	Both 3 times normal	Normal	1 normal April, 1960
5. F. K.	30	Second amenorrhea No menses 2 years	Severe	Primary	No	Yes	Normal	Normal	Normal	1 normal July, 1959 1 abortion Jan., 1960 Pregnant now
6. J. R.	24	Oligomenorrhea Menses 1 to 6 months	Mild	Primary	No	Yes	Normal	Normal	Normal	1 normal May, 1960
7. L. A.*	22	Oligomenorrhea Menses 3 to 6 months	Moderate	Primary	No	Yes	Normal	Slight enlargement	Normal	1 abortion 1 normal April, 1959
8. J. H.	24	Oligomenorrhea Delivery Oct., 1958, menses Jan. and July, 1959	Mild	Secondary	No	Yes	Normal	Right, 3 times normal Left, normal	Normal	Operation, Jan., 1960; now pregnant
9. R. B.	26	Oligomenorrhea Menses 1 to 3 months	Mild	Primary	No	Yes	Normal	Normal	Normal	Operation, Feb., 1960
10. L. T.	30	Oligomenorrhea Menses 3 to 7 months	Mild	Primary	No	Yes	Normal	Both 3 times normal	Normal	Operation, Feb., 1960

*Had prednisone therapy only.

section of the ovaries. The length of time these patients may go without menstruating is remarkable. Cases have been reported of amenorrhea of 7, 8, and 10 years' duration,^{9, 10} with prompt re-establishment of normal menstrual cycles following wedge resection of the ovaries. Some of these patients have polymenorrhea or even menometrorrhagia. This was noticed by Ingersoll¹¹ in 5 of his 37 cases, and by Stein in 8 per cent of his cases. One of our patients (Case 4) had had almost continuous bleeding for 10 years before the diagnosis was made.

The urinary excretion of follicle-stimulating hormone and estrogen and the basal metabolic rate are normal.¹² Basal temperature curves and endometrial biopsies demonstrate persistent anovulation. Endometrial biopsies by several investigators^{11, 13, 14} have shown the endometrium to be predominately in the early or midproliferative phase, but not infrequently hyperplasia or even atrophy is found.

Hirsutism occurs in approximately 50 per cent of the patients. Usually the hirsutism is mild, but sometimes it may be very extensive. Seven of our patients had some degree of hirsutism. One patient had to shave daily. Usually this type of hirsutism is associated with a normal excretion of 17-ketosteroids. Facial and lower extremity hirsutism in Case 8 is demonstrated in Figs. 1 and 2.

Obesity was once considered as being of common occurrence; however, more recent studies have shown that obesity is no more common in this syndrome than is found in the general populace. None of our patients was obese.

The demonstration of bilateral sclerocystic disease of the ovaries is the keystone in the diagnosis. The gross pathologic appearance of the ovaries is typical of this syndrome and it is the one finding consistently present in these patients. The ovaries have a smooth, pearly white, shiny capsule. Multiple small to moderate-sized, fluid-filled cysts beneath the thick cortical rind do not bulge up onto the surface of the ovary. The characteristic surface scarring and indentations of the normal ovary are missing. The general shape



Fig. 1. Case 8. Mild hirsutism of face.

and contour of the normal ovary are maintained. Almost all authors, including Stein, have consistently described the typical ovary in this syndrome as being from 3 to 4 times enlarged. In my series of 10 cases, however, 6 patients exhibited the typical ovarian picture of the syndrome except that the ovaries were about normal size or only slightly enlarged. In 2 other cases (1 and 8) only unilateral enlargement of the ovary was found. Two cases (4 and 10) showed typical



Fig. 2. Case 8. Mild hirsutism of thighs.

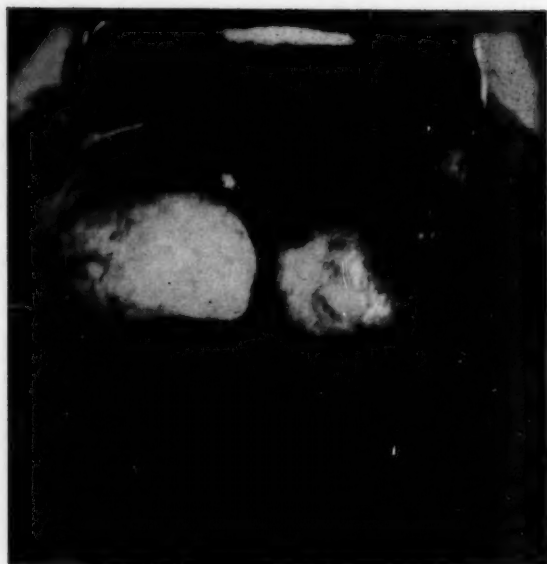


Fig. 3. Case 10. Bilaterally enlarged sclerocystic ovaries.

bilateral enlargement. Figs. 3 and 4 demonstrate bilateral ovarian enlargement in Case 10. Fig. 5 demonstrates the bilateral normal-sized sclerocystic ovary in Case 9. The left ovary is distorted by a 5 mm. endometrioma in the lateral pole. All wedge resection tissues in our cases were confirmed by the pathologist as "compatible with the Stein-Leventhal syndrome."

This finding has also recently been reported by Prunty, Brooks, and Mattingly¹⁵ and they state that "the impression is gained that only minimal enlargement, if any enlargement of the ovaries at all, need be present." Stein¹⁶ does not agree, and he states "the bilateral symmetrically enlarged ovaries are an essential part of the syndrome."

Can it be that the enlarged ovary is typical of the more advanced stages of the syndrome? Since the menses in all patients in our series returned to normal after therapy, and since 6 of the 7 patients who were followed became pregnant, it is definite that the diagnoses were correct. Possibly many patients with this syndrome are being overlooked because only those who have "enlarged" ovaries are investigated and submitted to wedge resection.

Pelvic examination, examination under anesthesia, or pneumoroentgenography, as

advocated by Stein, would fail to reveal the true diagnosis in the patient with the fairly normal-sized, sclerocystic ovary. The diagnoses in our patients were established preoperatively in almost every case by direct visualization by culdoscopy. This simple diagnostic procedure should be performed in every suspected case of Stein-Leventhal syndrome. Exploratory operation without preoperative confirmation either by gynecography or culdoscopy is unwarranted. Culdoscopy was performed in 6 additional patients suspected of having this syndrome, but direct visualization of the ovaries failed to reveal the typical gross appearance of the sclerocystic ovary. These 6 patients were spared an exploratory laparotomy for diagnosis.

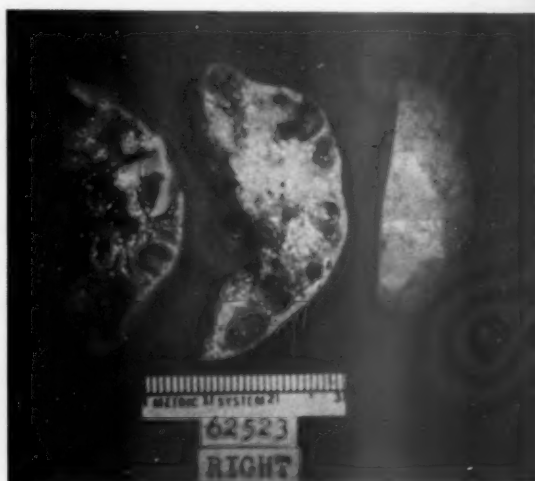


Fig. 4. Case 10. Wedge of right enlarged sclerocystic ovary.

Texas questionnaire survey

During review of this subject, several problems appeared which we felt could be investigated best by a questionnaire survey. Two hundred questionnaires were sent to the active members of this society. Admittedly, such surveys present many inadequacies. The conclusions drawn from the information received from respondents are, I feel, valid statements of trends. They are pertinent as answers to some of the questions encountered during the study.

Approximately 50 per cent of our membership responded to the unsigned questionnaire. It might be supposed that members who had no cases to report did not respond. Members having cases to report probably returned them because of greater interest. Only 33 per cent of our total membership reported having cases.

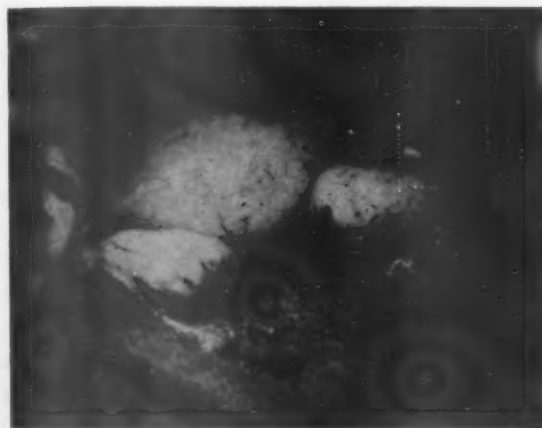


Fig. 5. Case 9. Bilateral normal-sized sclerocystic ovaries (small endometrioma distorting lateral pole of left ovary).

Fig. 6 gives the geographic distribution of the 217 cases of this syndrome in Texas as determined by the survey. Apparently, the ratio of reported cases is greater in our smaller than in our larger cities. Unfortunately, Fig. 6 also shows that 34 patients had an exploratory laparotomy at which the preoperative diagnosis was not confirmed. If direct visualization of the ovaries by culdoscopy had been utilized, possibly the 34 patients with the incorrect preoperative diagnosis would have been spared the laparotomies.

Culdoscopy was used for preoperative diagnosis in this syndrome only 30 times in the total of 217 cases. Over one half of all the culdoscopies were performed in Austin. Preoperative culdoscopies were reported from only 4 cities in the entire Texas survey.

Fig. 6 also shows only 61 patients became pregnant after wedge resection. This is a far different figure from that presented by Stein of 88.7 per cent pregnancies or 63

patients becoming pregnant of 71 married patients followed in his series. This estimate of the end result of our treatment in Texas indicates that possibly greater care should be exerted in making a positive preoperative diagnosis of this syndrome. It also indicates that probably a great many cases are being overlooked. More thorough, accurate investigation of sterile, amenorrheic, or oligomenorrheic women will establish a higher incidence of this syndrome.

Diagnosis

The standard diagnostic sterility tests must always be performed before subjecting a patient suspected of having the Stein-Leventhal syndrome to culdoscopy and finally wedge resection of the ovaries. An analysis of the husband's semen should precede all other diagnostic studies. Patency of Fallopian tubes should be established before proceeding further. Endometrial biopsy and thyroid function tests should be done. A 17-ketosteroid excretion determination should always be performed in suspected cases.

A diagnosis of Stein-Leventhal syndrome is made only after other causes of menstrual dysfunction, sterility, polycystic ovaries, and hirsutism are ruled out. Ovarian, pituitary, and adrenal gland diseases must be differentiated because they may produce one or more of the symptoms characteristic of the syndrome.

Perhaps the only pituitary condition to be seriously considered in a differential diagnosis is Cushing's disease, especially in its early stages. X-ray studies of the sella turcica for distortion, and of the cervical spine for osteoporosis are helpful when positive, as are the presence of cutaneous striae, typically distributed adiposity, and low metabolic rate.

Except for hirsutism, the presence of masculinization signs and symptoms are not typical of the Stein-Leventhal syndrome and, when present, they favor the diagnosis of either an adrenocortical disorder or one of the masculinizing tumors of the ovary. Most of the latter are unilateral tumors.

In the patient with suspected adrenal hyperplasia if the 17-ketosteroids or the

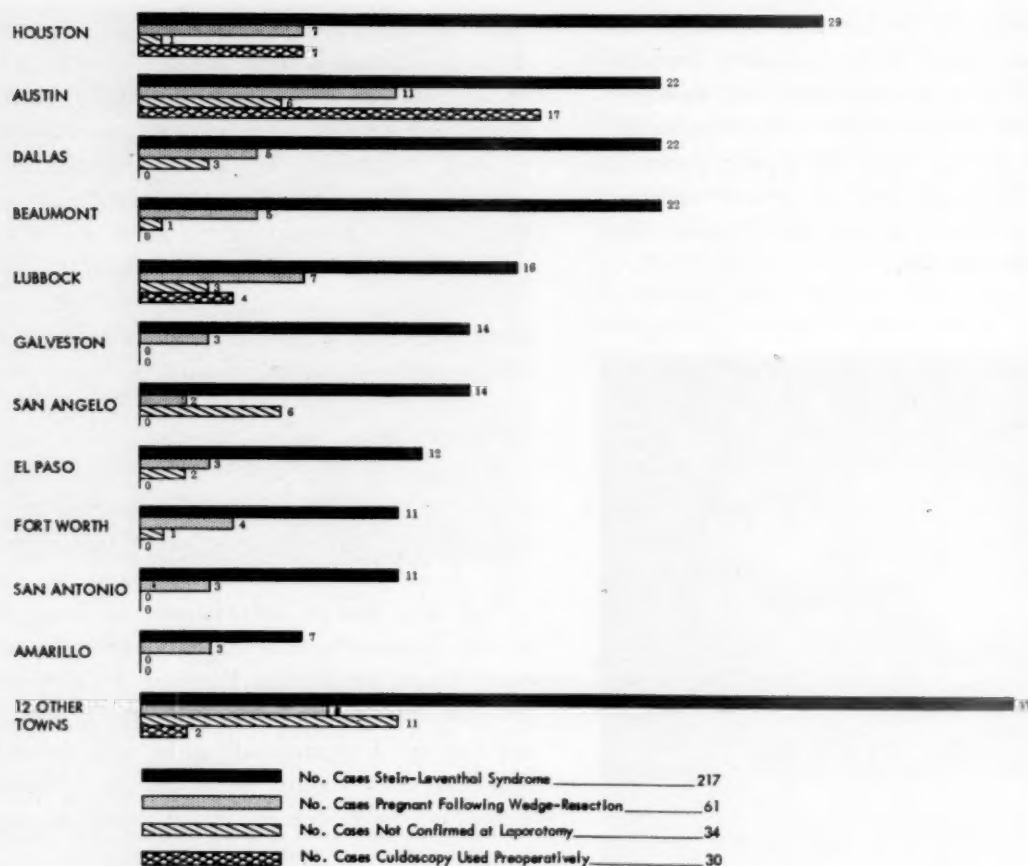


Fig. 6. Survey on Stein-Leventhal syndrome.

"pregnane complex" (mixture of urinary pregnandiol, pregnanetriol, and other related pregnanes produced by the ovaries and/or adrenals) or both are elevated, and the patient responds to prednisone therapy, a presumptive diagnosis of adrenal hyperplasia is established. Prednisone therapy should establish ovulation in this patient. The distinction between hyperplasia and tumor of the adrenal can be made from the fact that the adrenal tumor patient fails to show a decreased excretion level of the 17-ketosteroids following prednisone treatment.

In the group with "borderline adrenal hyperplasia" the diagnosis may be quite difficult since the ovaries are often about normal size, the hirsutism is mild, and the menstrual irregularities follow no definite pattern. Gold and Frank¹⁷ have found that these patients have a normal or only slightly elevated 17-ketosteroid excretion, but there is an elevation of the "pregnane complex" excretion

because of pregnanetriol. According to them if the "pregnane complex" falls after the administration of cortisone, a presumptive diagnosis of "borderline adrenal hyperplasia" is made.

If the 17-ketosteroids and "pregnane complex" excretions are both normal and culdoscopy reveals the typical sclerocystic ovaries, the probability of a good response to wedge resection is high.

In summary, the importance of unhurried study of each patient before resorting to operation cannot be overemphasized. In doubtful cases, a trial of prednisone therapy is advisable, and if it is marked by failure, then wedge resection may be indicated.

Endometrial carcinoma

Not until recently has emphasis been placed on the relationship between the Stein-Leventhal syndrome and development of endometrial carcinoma as a late complica-

tion. Speert¹⁸ in 1949 reported on several young women with endometrial carcinoma who had the syndrome, and since then others have reported similar observations. In 1957 Jackson and Dockerty¹⁹ reported on a group of 44 cases of the Stein-Leventhal syndrome in which 17 women had carcinoma of the endometrium. However, some of their cases were studied from a review of gross pathologic specimens and others from review of charts of amenorrheic, hirsute, obese patients so that the proper diagnosis of the syndrome in their patients is open to question. They regard carcinoma as a late complication. The 27 patients in their series who did not have endometrial carcinoma had had either wedge resection of the ovaries or bilateral oophorectomy performed. Those patients who had carcinoma had not had a wedge resection performed, and they also were several years older than those who did not have carcinoma.

Leventhal²⁰ states that neither he nor Stein has ever seen endometrial carcinoma in association with the syndrome. However, a wedge resection had been performed in all their cases. Despite their impression, Stein advocates that uterine curettage be performed in all cases, and if endometrial hyperplasia is found, the patient be followed carefully for carcinoma.

It may be that in patients with Stein-Leventhal syndrome, it is the untreated patient who may eventually develop carcinoma, but early wedge resection of the ovaries may interrupt this "chronic estrogen stimulation" of the endometrium and prevent the development of malignancy.

It is interesting to note that 4 cases of endometrial carcinoma associated with the Stein-Leventhal syndrome were reported in our Texas questionnaire survey. This is an incidence of about 2 per cent in the total of 217 cases reported. These are undocumented cases.

Treatment

The accepted treatment of this syndrome is bilateral wedge resection of the ovaries. Careful hemostasis is important. I know of

2 recent patients who have had to have oophorectomy some days subsequent to wedge resection because of severe interstitial ovarian hemorrhage.

Wedge resection is, as Bishop²¹ states, "as fantastically successful as it would appear illogical." Wedge resection restores the menstrual rhythm and ovulation in nearly 90 per cent of the patients and about two thirds of them become pregnant. There is little or no improvement of the hirsutism following operation. Recurrence of the condition following wedge resection is rare.

Numerous reports in the literature present the results of treatment of young, unmarried patients with the Stein-Leventhal syndrome. Is it wise to treat a single person by operation just to improve the regularity of menstruation? To my mind, it would be wiser for the surgical procedure to be postponed until after marriage when the wedge resection can be done to correct the patient's infertility. Young, unmarried women with menstrual irregularities respond to reassurance and simple explanations of the physiologic basis of their menstrual problems, and they readily accept the suggestion that definitive investigation and treatment be postponed until after marriage and the time that pregnancy is desired. It is my impression that conception is most likely to occur in the first few months following operation.

Conclusions

Wedge resection of the ovaries for treatment of the Stein-Leventhal syndrome should be limited to married, infertile women. There is little justification for wedge resection in a patient who has a sterile husband or who has bilateral Fallopian tube closure unless she has menometrorrhagia as a presenting complaint. It is suggested that wedge resection in the unmarried patient be postponed until after marriage and the time that pregnancy is desired unless menometrorrhagia is the primary complaint.

Culdoscopy for direct visualization of the ovaries before operation should always be performed if possible. Many exploratory laparotomies for the purpose of diagnosis

would be eliminated by this simple, easily performed diagnostic procedure.

Determinations of the urinary excretion of 17-ketosteroids and the "pregnane complex," and the use of the "cortisone suppression" test are valuable aids in the selection of patients for wedge resection.

All documented cases of endometrial carcinoma associated with the Stein-Leventhal syndrome should be reported in order that we may more adequately assay the relationship between the two conditions. It would seem unwise at the present time to assume

that the Stein-Leventhal syndrome is a precursor of endometrial cancer and advocate wedge resection as prophylaxis.

My experience indicates that the ovaries in the Stein-Leventhal syndrome do not necessarily have to be enlarged. If the other diagnostic criteria typical of this syndrome are present, and culdoscopy reveals the typical gross appearance of the Stein-Leventhal ovary, even though it is of normal size or only slightly enlarged, then wedge resection is indicated and will probably produce the desired result.

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Discussion

DR. JOHN A. WALL, Houston, Texas. I want to congratulate Dr. Blewett on this timely presentation. I admire his tenacity and presentation of a current problem from which many varied ideas must be assimilated. He has done this work with his usual thoroughness and has adequately analyzed his experience.

Data on steroid chemistry are appearing much more rapidly than we are able to comprehend and apply clinically. We are in a phase of development with regard to clinical endocrinology. The difficulty of communication between the steroid chemist and the clinician demands teamwork. Steroid chemistry is complex, progress is rapid, and biologic assays are still paramount.

It appears to me polycystic ovarian enlargement is a progressive syndrome and not a disease entity. Consequently, many of us are observing this condition in different phases of development. It does not appear to me to be a primary ovarian problem. This is emphasized by the report of the association with adenocarcinoma of the endometrium in younger women. The principal deduction in this instance is that this relationship is more than coincidental. Possibly it represents an imbalance between the follicle-stimulating hormone (FSH) and luteinizing hormone (LH), supposedly derived from the beta cells of the anterior pituitary gland. This may be a consequence of an imbalance between the pro-

portions of FSH and LH; the sequence of release; or possibly the major threat may be through the adrenocorticotrophic effect.

There would, therefore, presumably be some basis for indicting the progesterone metabolism of the adrenal gland and its consequent effect on the endometrium. Drs. Ray Kaufman, Jack Abbott, and I reported a study of the endometrium in 17 women with the Stein-Leventhal symptom complex. The clinical response, evidenced by resumption of normal menstrual function in 15 of the 17 patients following wedge resection of the ovaries, represented 88 per cent return of cyclic menses. Six of the 10 demonstrating endometrial hyperplasia preoperatively revealed no evidence of this histologic picture following ovarian resection. Two of the 3 with atypical hyperplasia before treatment had a return to normal following operation. The third, following evidence of return of ovulatory periods on one occasion, again demonstrated the atypical endometrial hyperplasia noted before resection. This patient at the time of the report was 36 years of age and may fit into that group that has not received treatment early enough and whose endometrial changes are no longer reversible. Therefore, my own feeling is that there seems to be increasing evidence that there is an elevation of the pituitary LH in the Stein-Leventhal syndrome, or at least an abnormal LH production.

Indeed some postulate that there is a primary adrenocortical metabolic defect which leads to low serum corticoids, increased pituitary ACTH production, and consequent increase in the elaboration of adrenocortical androgen which inhibits the pituitary and so results indirectly in influencing ovarian metabolism producing the concomitant ovarian follicle cysts. The fact that Dr. Blewett has found the ovaries to be of normal size or only slightly enlarged and yet the women have fulfilled all the criteria for Stein-Leventhal changes has been verified by other observers. I think this only proves that we probably are dealing with different phases of the same progressive polyglandular endocrinopathy.

I have reported on 2 patients with chromophobe adenomas of the pituitary associated with endometrial cancer. Both were blind and weighed over 240 pounds and only one was followed through to autopsy. This woman had hypertension and hirsutism and presented the buffalo hump characteristic of Cushing's syndrome. Following the diagnosis in 1953 of adenocarcinoma of the endometrium, I treated her with radium.

Operation was not performed because of her physical handicaps. She lived for two years following this treatment but died after developing diabetes during the last 6 months. Autopsy revealed a chromophobe adenoma of the pituitary and extreme hyperplasia of the adrenals which weighed a total of 79 grams as contrasted with the normal high of 15. There was no residual tumor in the uterus but metastatic carcinoma was found in the liver. The ovaries were atrophic, possibly from radiation, and stromal cellularity and numerous corpora albicantia were noted.

DR. JAMES G. STOFFER, Ft. Worth, Texas. Dr. Blewett is to be commended for bringing us this most enlightening study of the Stein-Leventhal syndrome. He has called to our attention, however, that we in Texas are not doing very well in making an accurate diagnosis before operation. The fact that 34 cases out of 217 were not confirmed at laparotomy should make us sit up and take notice. This means nearly 16 per cent of the cases operated upon failed to have the polycystic ovaries of Stein.

In the literature of the Stein-Leventhal syndrome it appears that the important thing about the etiology is that this disorder must lie within the ovary itself, because resection of the ovaries affords the cure with a minimum opportunity of recurrence.

Dr. Blewett's incidence of 10 cases in 5 years bears out the importance of the fact that this is indeed a relatively infrequent condition. Dr. Stein's own experience based on his published figures averages out to about 4 cases per year.

Most investigators have stressed that the key-stone to the diagnosis is enlargement of the ovaries. Dr. Blewett shows us that this is not necessarily so, for 6 of his 10 patients did not exhibit enlarged ovaries. The successful results attained following ovarian resection in these cases would certainly bear out this point. The suggestion that the enlarged ovary may be typical of the more advanced stages of the syndrome is well taken and is worthy of further investigation. Indeed, many patients with this syndrome may well be overlooked because they do not have enlarged ovaries.

In diagnosing the Stein-Leventhal syndrome, emphasis should be given to the cortisone test. This is done by giving 100 mg. cortisone four times daily (or a substitute in equivalent dosage) 4 to 16 days and observing for a fall in the 17-ketosteroids. Those cases with slight or moderate

elevations of the 17-ketosteroids should receive this test, lest one make a faulty diagnosis in cases with borderline adrenal hyperplasia. Wedge resection of the ovaries will be of no value in such cases. Likewise it should be pointed out that Jones found some of his cases of Stein-Leventhal had moderate 17-ketosteroid elevations and responded initially to cortisone treatment. Ovulation was produced; however, the effects were transitory, and suppression was not maintained. This would be attributed to a temporary shift of the adrenal-ovarian-pituitary relationship, and it was not real evidence of associated adrenal pathology.

I agree that visualization of the ovaries should be made prior to subjecting these patients to laparotomy. The exception to this, of course, is the unusual patient in whom repeated pelvic examination reveals palpable bilateral ovarian enlargement. I have found posterior colpotomy with its direct visual and palpatory means to be more satisfactory than culdoscopy. The culdoscope should be reserved for those who have obtained adequate training and practice to have developed

proficiency in its use. It is not as simple as it would appear. Admittedly my experience with the culdoscope has been limited, but I have used it many times and have found it to be more difficult than posterior colpotomy. I believe colpotomy adds little if anything to the discomfort or morbidity of the patient.

Once the diagnosis of the Stein-Leventhal syndrome is made I do not believe treatment should necessarily be limited to married infertile women for the following reasons: (1) recurrence following wedge resection is rare; (2) many times it may be more feasible to solve these problems before marriage to assist in re-establishment of the menses and reassure the patient of the likelihood of future fertility; (3) frequently these girls may be in a better socioeconomic position to undergo treatment prior to assuming the responsibilities of marriage; (4) the possible association of endometrial carcinoma with the Stein-Leventhal syndrome appears to occur in the patient who has not had wedge resection of the ovaries, apparently the result of prolonged steroid stimulation.

Myoma of the cervix

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SINCE total abdominal hysterectomy has become the operation of choice whenever the removal of a uterus is indicated, the problem of a malignant or benign lesion of the remaining cervix has decreased. Carcinoma of the cervix, the most common type of malignancy of the genital tract, is reported to appear in 3 per cent of the patients with retained cervical stumps. According to Te-Linde¹¹ this percentage has been incorrectly quoted, and from his experience should be much lower. Although myoma of the cervix is the most frequent benign tumor, except polyps, even in the intact uterus, it is comparatively rare. This is emphasized by Hyams¹⁴ observation in which only two such instances were found in 1,800 patients who had had a previous supravaginal hysterectomy.

In order to determine the frequency of cervical myomas a survey was made of patients operated upon for fibromyomas at the Hospital for the Women of Maryland. The case histories, physical and pelvic findings, as well as the operative records and pathologic reports were scrutinized in 1,068 patients who were admitted for definitive operative therapy from 1948 to 1958, inclusive. The symptoms, location, type of tumor, physical and pelvic findings, and the operative procedure were studied carefully. In this series 3 were found to have cervical myomas. One patient was aged 50, another 45, and the third 28. The first patient (aged 50) had irregular vaginal bleeding over a period of 4 to 5 years. She was also found

to have associated corporeal fibromyomas. The treatment consisted of a total abdominal hysterectomy. The other 2 patients (aged 45 and 28) had no symptoms relative to their cervical lesions.

The tumors in both instances were discovered upon speculum examination. The myomas were small, discrete, single, and were not accompanied by similar tumors of the other portions of the uterus. The treatment here was conservative and limited to local excision. In the remaining 1,065 patients who had myomas of the uterus, 88 had myomectomies, 174 vaginal hysterectomies, 562 total abdominal hysterectomies, 83 subtotal hysterectomies, and 158 were discharged without operation. Subsequent examinations revealed no tumors of the retained stumps.

Solid benign connective tissue and muscle tumors of the cervix were reported as early as 1859. Since then there have been scattered reports throughout the literature. The incidence is said to be from 0.42 to 15.5 per cent.³ The majority of pathologists agree that a more likely figure would be in the neighborhood of 8 per cent. The discussion of this subject matter is limited. However, a thorough study was carried out by Counseller and Collins¹ in 1935. Their data include the findings in 112 previously reported cases and describes in detail an interesting case of their own. Similar studies were made by Hyams,⁴ Torpin,¹² and Torpin and Beard.¹³ Scott and Spence⁵ in 1951 report an unusual case of submucous cervical myoma complicating a 22 week pregnancy. Sites, Coury, and Baruss¹⁰ published a case report in 1956 of a cervical myoma simulating an ectopic pregnancy. No one author

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has been able to collect a sizable series of his own, which in itself attests to the infrequency of occurrence.

The causes of the production of cervical myomas or fibroids of the uterus in general are unknown. Fibroids are most common in the uterine wall, the ratio of their appearance to that in the cervix being 5 to 95.⁷ Virchow¹⁶ believed that any muscle fiber in the uterus could form a myoma as the result of some unknown stimulation. Meyer⁶ was of the opinion that the tumors arose from club-shaped swollen muscle bundles which in turn are transformed into small nodules which eventually become fibroids. Others claim origination from special myoblasts, epithelial cells, or the musculature of blood vessels. No one theory has gained universal acceptance. In recent years there is some experimental and clinical evidence that growth and production of fibromyomas are influenced by estrogens.

In 1950 Lipschutz⁵ was able to induce fibroma in experimental animals with the administration of estrogens. Shute,⁹ as well as Torpin, Pund, and Peeples,¹⁴ in clinical studies of fibromyomas of the uterus, were convinced that estrogen played a part in the genesis of this disease since they are observed during the active sex and productive life of women. Timonen and Purola,¹⁵ in a study of 391 patients with myomas, revealed that hyperestrogenism, determined by vaginal cytology, is frequent (56 per cent). They also hypothesized that other etiological factors may be present, such as a disturbance of the neurovegetative balance, and that distention caused by the tumor itself could accelerate the growth process. Fluhmann's² intensive investigative studies of the cervix revealed that the mesenchyme from Müllerian structure constitutes the basis for the uterovaginal primordium. It is from these cells that connective tissue and muscle of the uterine corpus and cervix developed. Therefore, it seems plausible that the factors inherent in the production of fibroids of the uterine body may well be the same as those that create a similar tumor of the cervix. If the mechanisms produce a hyperplastic

reaction, myomas are apt to develop, while carcinoma may result if mutation of the cells occurs.

Fibromyomas of the cervix are usually single and have a tendency to grow slowly. From the examination of the published data, most of these tumors are not discovered unless they are accompanied by profuse hemorrhage, abdominal enlargement, protrusion from the vagina, or produce obstruction in labor. The most common symptoms are bleeding, vaginal discharge, and pelvic discomfort. When the tumor reaches considerable size, pressure symptoms such as urinary frequency, retention, or constipation can result.

The Torpin and Beard¹³ classification of myomas of the cervix is classical. They list 4 varieties as follows: (1) those in the upper part of the cervix that grow into the abdominal cavity, (2) those that originate in the vaginal portion and eventually enter the vagina, (3) those that originate in the mid-portion and enter the broad ligament or extend anteriorly or posteriorly, and (4) those that take origin from the stump after the supracervical hysterectomy. An additional case report is added to the literature that appears to fall into the second category.

Case report

Mrs. E. M. entered the hospital with a history of marked vaginal discharge and bleeding of 4 years' duration. She had had two full-term pregnancies and one early abortion of a fetus of about 4 to 6 weeks' gestation. All of the postpartum courses were uneventful. The menses began at 13 years, appeared every 5 to 6 weeks, and lasted about 4 to 5 days. The periods were not associated with pain. About 4 years prior to the present illness the patient began to have irregular vaginal bleeding. The periods lasted longer and were more profuse; because of this a curettage was performed. The microscopy examination of the tissue removed revealed fragments of proliferative endometrium. Since operation the periods became fairly regular but occasionally there were episodes of intermenstrual bleeding. The vaginal discharge became profuse. She was treated for Monilia-Trichomonas type of vaginitis, but the discharge persisted. The

cytologic examinations were negative for malignancy. On two occasions a thorough biopsy of all of the quadrants of the cervix was done and these revealed no malignant elements. An electrocauterization of the cervix made little difference in the appearance of the organ. The cervix remained hypertrophied, bled readily upon touch, and emitted a discharge continually.

The family, past, and systemic histories were noncontributory. A physical examination revealed a well-developed white woman not in acute distress. The secondary sex characteristics were well developed. The somatic examination showed no positive physical findings.

The pelvic examination revealed a marital outlet. The Bartholin and the Skene glands, and the urethra were without abnormality. There was no cystocele, rectocele, or prolapse. The cervix appeared hypertrophied, lacerated, and bled readily upon touch. The uterus was normal in size for a multipara, freely movable, and in an anterior position. There were no palpable masses in either adnexal region. Because of the persistence of symptoms, a more thorough surgical exploration of the cervix was considered necessary.

At the time of operation the pelvic findings were confirmed. A Sturmdorf amputation of the cervix and dilatation and curettage were performed. The endometrial scrapings revealed endometrium in the proliferative phase as well as an endometrial polyp. The microscopic examination of the cervical specimen showed an intracervical myoma with chronic cervicitis.

The patient made an uneventful postoperative recovery. Upon follow-up examination, the

cervix was healed; there was no evidence of laceration, erosion, or discharge.

Comment

From our own experience and the reports in the literature, it is evident that myomas that originate in the cervix, either in the cervical stump or the intact uterus, are uncommon. These tumors are not found under ordinary circumstances, but usually are detected when they extend into the abdomen, produce severe hemorrhage, protrude from the vagina, or obstruct labor. Our patient had a cervical myoma that was discovered only after amputation of the cervix was performed to cure a severe irritating vaginal discharge. The events accentuate the necessity for conization of the cervix rather than multiple biopsy in obtaining an adequate appraisal of cervical pathology.

Summary

1. The literature concerning benign connective tissue tumors of the cervix is surveyed.
2. The various types of cervical myomas are noted.
3. An additional case report of a cervical myoma is added to current literature.
4. The necessity of performing conization is stressed in preference to biopsy for an adequate picture of cervical pathology.

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Fibromyoma of the Fallopian tube

Report of a case and review of the literature

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FIBROMYOMA of the Fallopian tube is an extremely rare tumor.^{8, 11} In the previous 53 cases reported in medical literature,¹⁻³⁷ the specific diagnosis of fibromyoma of the tube has never been made prior to operation.^{1, 23}

It is strange that a fibroid of the tube should be rare when uterine fibroids are so common.^{6, 30} Embryologically, both the uterus and the tubes arise from the Müllerian ducts, yet primary tumors of the uterus are as common as primary tumors of the tube are rare.^{17, 20} The extreme cyclic changes in the uterus associated with menstruation and pregnancy and the comparative nonreactivity of the tube may explain the difference in the incidence of the neoplasm.^{6, 7}

Pathology

Leiomyofibromas of the tube are usually fairly small although one was reported which weighed 2 kilograms.³⁴ These tumors are usually single.⁵ They may be subperitoneal, interstitial, or submucous.^{5, 26, 28, 35} However, the tumor most often arises from the pars interstitialis. Tumors originating in the ampullary portion of the tube are extremely rare.¹⁷

Tuberculosis has been described as being associated with a tubal fibroid too often to be coincidental.^{25, 34} Torsion of the tube

and ectopic gestation have also been concomitant findings.^{32, 34}

Grossly the fibroid of the tube has been clinically identified and confused with adenomyomas and nodules of salpingitis nodosa.

Strangely, most of the reported cases have been found on the left side,⁵ as is our present reported case.

Cystic degeneration,^{1, 18} purulent changes,³⁶ calcification,^{9, 27} myxomatous degeneration,^{17, 25} and hyalinization of the tubal fibromas have been recorded. They frequently coexist with uterine fibroids.^{23, 24}

Histologically these tumors show the same structure and undergo the same degenerative changes as fibroids in any other location.^{5, 34}

There are no pathognomonic symptoms.^{5, 34} Menstruation is not affected.⁵ Torsion will cause the expected dramatic episode of pain typical of torsion of any pelvic structure.^{1, 5, 14, 16, 17, 27} Pelvic complaints are usually due to accompanying pathologic conditions rather than to the fibroid of the tube itself.

A hard, smooth, mobile, nontender swelling of the tube can usually be palpated upon pelvic examination.⁵ The finding of the fibroid during surgical intervention is usually misdiagnosed as some other more common abnormality of the involved adnexa.

The treatment is surgical removal.⁵

Case report

Mrs. E. F. P., a 58-year-old white married woman, was examined on Aug. 24, 1959, and

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treated for an acute pyelocystitis. Pelvic examination revealed an ovoid, firm, but slightly doughy mass $3\frac{1}{2}$ by 5 cm. in size in the left adnexal region. At that time it simulated an enlarged ovary displaced anteriorly.

On Sept. 15, 1959, findings on urine examination were normal. There was no pain. The ovoid mass was 5 cm. in diameter, doughy, and very slightly tender. It was not as tender as an ovary should be and yet it was separate from the uterine fundus. A diagnosis was made of tumor mass in the left anterior adnexal region which could be a pedunculated fibroid or tumor of the ovary. Re-examination was advised for 2 weeks later.

On Sept. 30, 1959, the tumor, now approximately 8 by 5 cm., was easily felt in the left anterior adnexal region and surgical intervention was advised to rule out carcinoma of the ovary.

A laparotomy was performed on Oct. 5, 1959. The uterus was small, anterior, and regular in appearance. The right tube was patulous and normal. The right ovary was small, atrophic, and normal. Arising from the middle portion of the left tube, 3 cm. from the uterine cornu, was an ovoid, firm, smooth tumor mass 4 by 5 cm. in diameter. The tube entered this firm fibroid-like tumor and continued out the distal portion of the tumor for 4 cm. After removal, the tumor was opened and had the gross appearance of a

fibroid tumor arising from the wall of the Fallopian tube. The left ovary was small and atrophic. There were a few loose adhesions from the omentum to this area. The remainder of the pelvic structures were normal.

Total hysterectomy and bilateral salpingectomy were performed. The appendix had previously been removed.

The pathology report stated that the left uterine tube was markedly distorted by a smooth-surfaced, oval, rubbery, firm 7 by 5 by 5 cm. nodule. Serial cross sections showed that this nodule appeared to arise from the tubal wall and at some points it was almost impossible to trace the lumen of the tube. Cut surfaces of this nodule showed a whorled, white pattern but there was less bulging at the margins than is usually seen in fibromyomas of the uterus. No additional gross lesion was recognized in the tube.

Microscopically, section of the nodule attached to the uterine tube showed the characteristic whorled and angular pattern seen in fibromyomas.

Summary

A case of fibroid tumor of the left Fallopian tube has been reported and the literature reviewed. This review encompasses the 53 previously reported cases.

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Massive intraperitoneal hemorrhage due to uterine fibroids

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THE variable behavior of uterine fibroids is well recognized. Almost every conceivable pathologic manifestation of these tumors has been encountered. Excessive uterine bleeding is often associated with fibroids. Intraperitoneal bleeding of major magnitude due to a nonpedunculated subserosal benign fibroid is a rare phenomenon. It is nevertheless a definite clinical entity.

Carl von Rokitansky¹ first accurately described the picture in 1861: "Large or multiple fibroids effect a pressure on . . . the uterus itself . . . and hence an enlargement of the blood vessels which may be even further stretched and occasionally be torn. In this manner it has been noted that a tear of subperitoneal vein of a fibroid has led to hemorrhage into the peritoneal cavity."

Since this original description a century ago approximately 50 cases have been reported in the American and European literature. In every instance the bleeding has occurred from torn, enlarged veins coursing over the surface of subserous fibroids. The bleeding has invariably been persistent and of massive proportions in all cases in which exploratory operation was performed. A clinical picture of sudden and profound hypovolemic shock with severe abdominal tenderness has often forced the surgeon to perform an emergency laparotomy without a definite diagnosis. In most cases the critical condition of the patient has then prompted an emergency subtotal hysterectomy. Because of the serious nature of this rare clinical

entity, a case recently encountered is being reported here.

Case report

K. G., a 34-year-old, para i, white woman, separated from her husband, entered the Emergency Ward of the Massachusetts General Hospital at 8:30 P.M. on March 21, 1959, with the chief complaint of the sudden onset of lower abdominal pain. About 30 minutes prior to admission to the Emergency Ward she had been standing in her home when she noted sudden severe lower abdominal pain. She felt faint and went to bed. The pain became steadily worse, but remained localized in the lower abdomen and suprapubic region. There was no history of any trauma, and recent exposure to pregnancy was denied. She had had a normal pregnancy and delivery 8 years ago. Her last menstrual period had been a month prior to admission and on the previous day a normal cycle began.

She had had a cholecystectomy for cholelithiasis performed at this hospital 8 years before admission. Abdominal exploratory operation at the time of cholecystectomy had revealed a small but normal uterus, normal ovaries, and tubes. She had been in good health since, but for about a year she had noted occasional postprandial epigastric hunger pains relieved by milk and antacids. Her system review was otherwise entirely normal.

Physical examination revealed a pale moderately obese young woman in severe distress. Her blood pressure was 110/80; pulse, 104; respiration, 20; temperature 101.4 F. per rectum. Physical examination was within normal limits. The abdomen was exquisitely tender, particularly in both lower quadrants and the suprapubic

region, preventing satisfactory deep palpation. There was moderate spasm and rebound tenderness. Peristalsis was absent. Pelvic and rectal examination gave the impression of a fullness in both adnexal regions; the cervix was closed, firm, and very tender on motion. There was a slight bloody ooze from the cervical os consistent with menstrual flow. The extreme tenderness and moderate obesity of the abdomen precluded satisfactory palpation for the uterus and the ovaries. No abnormal masses were detected, however, on this limited examination.

The hemoglobin level on admission was 13.6 Gm. per cent, and white blood count, 18,300 with a normal differential. Clotting time and bleeding time were within normal limits, platelets appeared adequate in number and quality on a blood smear. Urinalysis was negative. Amylase level was 4 Russell units (normal 18 to 20 units). Gastric aspiration recovered clear fluid with free acid present and no occult blood. A peritoneal aspiration in the right lower quadrant recovered 30 c.c. of dark blood which would not clot. Stool guaiac was negative.

While being prepared for laparotomy her blood pressure dropped to 70/50 with the pulse rising to 120 per minute. She was transfused rapidly with 500 c.c. of whole blood and 250 c.c. of plasma with some improvement of her circulatory status. With a preoperative diagnosis of ruptured ectopic pregnancy, or intra-abdominal bleeding from undetermined site, laparotomy was performed under general anesthesia. The peritoneal cavity was filled with dark blood. A rapid exploration of the upper abdominal organs was carried out without encountering any abnormality. The ovaries, tubes, and appendix were normal. On top of the uterine fundus, which was not enlarged, there was a solitary fibroid about 7 cm. in diameter. A little over one half of this subserosal fibroid was projecting above the surface of the uterus, the other half still imbedded within the myometrium. At the periphery of the fibroid, at its junction with the uterus, the serosal covering was sharply delineated as a circular constricting band. Overlying the dome of the fibroid were a few thin-walled enlarged veins about 0.5 cm. in diameter. There was a tear in one of these veins with a steady flow of blood from it. No other source of bleeding was encountered. Rapid suture of the ruptured vein was carried out with control of the hemorrhage. The free blood in the peritoneal cavity was evacuated, the patient being trans-

fused in the meantime with whole blood. Since her condition remained stable, a myomectomy was carried out without entering the uterine cavity. The abdomen was closed in layers. She received in all 4,000 c.c. of whole blood from the time of admission to the Emergency Ward to the termination of the operation. The post-operative course was uncomplicated.

The pathologic report described a sharply circumscribed, discrete, and roughly spherical leiomyoma 7 cm. in diameter with fresh hemorrhage dissecting the leiomyoma from the overlying serosa.

Comment

In 1922, in a comprehensive study of "influence of myomata on the blood supply of the uterus, with special references to abnormal uterine bleeding," John A. Sampson² found by injection studies that the subserous location of a fibroid changed the vascular pattern of the uterus considerably. While the uterus itself is not deprived of its blood supply, a significant portion of the uterine arterial supply is shunted into the tumor. The venous drainage of these tumors is via dilated veins coursing over their surface and entering large venous channels at the periphery of the supporting myometrium. He found that these prominent superficial veins were for the most part associated with subserosal fibroids of 10 cm. or more in diameter. The presence of dilated and/or tortuous, thin-walled veins overlying uterine fibroids which are not pedunculated is not an uncommon observation during routine abdominal or pelvic operation. The potential danger of massive bleeding from these exposed veins, is however, not always apparent to the surgeon. These particular subserosal fibroids are neither infarcted, necrotic, hemorrhagic, or malignant. In fact, one is hard put to account clearly for the mechanism which precipitates the bleeding from vessels which must have been there for quite a while. Trauma seems, on first thought, to be a likely cause. Indeed, trauma in the form of a fall, exertion or even abdominal massage has been frequently, though not invariably, mentioned as preceding the bleeding episodes in the reported



Fig. 1.

cases. Many, though not all, patients have bled at the onset or during their menstruation. The implication is that the uterine vascular engorgement during menstruation had led to distention of these vessels to their breaking point.

Another possible cause for sudden hemorrhage is suggested by the local findings in the case reported here. As seen in Fig. 1, the fibroid tumor seems to be pushing itself out of the myometrial confines. The force of this extrusion process has created a sharp demarcation line around the circumference of the fibroid where it is projecting above the myometrium. The force of tension created on the surface may have led to the tear of the superficial vein.

The description of those cases occurring either during pregnancy or immediately after parturition is compatible with either of the two theories, i.e., increased blood flow, or mechanical extrusion.

The correct diagnosis has been made very rarely preoperatively. Ruptured ectopic pregnancy or corpus luteum cyst, etc., and finally "intra-abdominal bleeding of unknown source" are the common preoperative diagnoses. The presence of a large pelvic tumor discovered on physical examination or a history of such a tumor might be a helpful hint, but, as in our case, there may be no clue to the presence of a fibroid beforehand. The severe tenderness and rigidity of the abdomen at the time of hemorrhage often precludes definite detection of a fibroid on physical examination.

The clinical entity of idiopathic hemoperitoneum should be mentioned in this regard to emphasize the unpredictable and catastrophic nature of this condition. Many of the cases reported in the literature under the heading of idiopathic intra-abdominal hemorrhage had no bleeding site demonstrated at laparotomy. Without intending to question the proper classification of most of these cases, we wonder if in some of these instances the bleeding might not have been from a tear of one of the smaller subserosal veins of a uterine fibroid. The rate of blood loss apparently bears no relationship to the size of these veins. A careful search for these veins is warranted in all instances of intraperitoneal hemorrhage where the source of blood is not immediately apparent at operation.

The surgical procedure carried out in most cases is aimed primarily at control of the life-endangering hemorrhage and a supracervical hysterectomy or "fundectomy" is often hurriedly performed. Some surgeons advocate rapid suture of the bleeding vessels, deferring hysterectomy to a later date. That myomectomy can be performed with satisfactory control of bleeding and salvage of the uterus has been shown in the past^{3, 4} and is demonstrated in this report. It certainly is the ideal procedure when preservation of the childbearing function is important for the patient concerned.

In 1922 Ernst and Gammeltoft⁵ summarized the world literature pertaining to this entity and described 2 additional cases of their own. Five of these patients had pedunculated fibroids and in one instance the bleeding site was not related to the tumor. These 6 cases are, therefore, discarded, leaving a total number of 17 acceptable cases reported prior to 1922.

The accompanying table presents a summary of the cases reported since 1922. It begins with the 2 cases of Ernst and Gammeltoft which were not included in their summary. Although more have been reported⁶ we have included in our series only those that met our criteria of selection. In some of those omitted the bleeding had occurred

Table I. Cases reported from 1922 to 1957

Author	Age	Parity	Menstrual history	Previously known pelvic tumor	Preceding trauma	Severity of shock	Pelvic tumor palpable on admission	Time from onset of illness to operation
1. Ernst and Gammeltoft ⁵	40	0	Infrequent periods		Traffic accident	Severe	Yes	4 hours
2. Ernst and Gammeltoft ⁵	30	i	Last period 3 months previously		Overstraining of back and of abdomen	None initially, severe shock within 24 hrs.	No	24 hours
3. Breitner and Schönbauer ⁷	46			Yes	None	Moderate to severe		Few hours
4. Kunz ⁸	44		Onset of normal period 1 day previously		None	Severe	Yes	8 hours
5. Alexander ⁹	33	i	Normal		None	Slight initially, sudden severe shock 2 days later	Yes	2 days
6. Alexander ⁹	36	0			None	Severe	Suggestive	Few hours
7. Hoffmann ³	25	i	Full-term pregnancy	Detected at 2nd gestation month	Uneventful vaginal delivery 1½ days previously	Moderate to severe		2 days
8. Brakemann ¹⁰	40	ii	Onset of normal cycle		None	Minimal	Yes	Few hours
9. Arnould ¹¹			Normal vaginal delivery 36 hours previously	Yes	None			24 hours
10. Polacco ¹²	50	ii	Frequent metrorrhagia	Yes	Washing clothes	Moderate to severe	Yes	Few hours
11. Mestitz ⁴	38	i	Fifth month of normal pregnancy		Washing clothes	Moderate		None
12. Imholz ¹³	42					Progressive and severe		
13. Herzfeld ¹⁴	33	0	Normal	Yes	Abdominal pain after coitus	Mild	Yes	days
14. Shapira and Starr ¹⁵	37		Last normal period recently completed		None	None initially	Yes	days

<i>Pelvic tumor palpable on admission</i>	<i>Time lapse from onset of illness to operation</i>	<i>Preoperative diagnosis</i>	<i>Operative findings</i>	<i>Operation performed</i>	<i>Results</i>
Yes	4 hours	Rupture of intraperitoneal vessel or cyst	Large quantity of intraperitoneal blood, large irregular fibroid with many subserosal torn veins	Hysterectomy and appendectomy	Recovered
No	24 hours	Twisted ovarian cyst, extrauterine pregnancy with hemorrhage	Free blood in peritoneum, ruptured vein on posterior wall of large fibroid 10 weeks intrauterine pregnancy	Supravaginal hysterectomy	Recovered
	Few hours	Extrauterine pregnancy, idiopathic intraperitoneal bleeding	Free intraperitoneal blood, multiple subserosal fibroids rupture of 1/2 cm. superficial vein	Suture of ruptured vein, extirpation of uterus 6 weeks later	Recovered
Yes	8 hours	Rupture of subserosal vein of fibroid	Free peritoneal blood, fibroid the size of two fists with posterior aggregation of superficial veins with bleeding	Suture of bleeding veins	Recovered
Yes	2 days		Free intraperitoneal blood, large fibroid with ruptured vein on surface	Supravaginal amputation of uterus	Recovered
Suggestive	Few hours	Ruptured vein from myoma	Free intraperitoneal blood, fibroid size of child's head with ruptured superficial vein	Right salpingectomy and supravaginal hysterectomy	Recovered
	2 days	Bleeding from fibroma	Free intraperitoneal blood, solitary fibroid with torn vein on surface; fibroid 11 cm. diameter	Myomectomy	Recovered
Yes	Few hours	Uterine fibroid, intraperitoneal bleeding	Solitary fist-sized fibroid with rupture of one of many subserosal veins	Total extirpation with removal of ovaries and tubes	Recovered
	24 hours	Intra-abdominal bleeding	Large quantity of blood in peritoneal cavity from subserosal veins overlying the fibroid (size of an orange)	Subtotal hysterectomy	Recovered
Yes	Few hours	Fibroid, torsion of cystic ovary	1.5 L. of blood in peritoneal cavity bleeding from rupture of thin-walled finger-sized venous sinuses over fibroid	Supravaginal hysterectomy	Recovered
	None		Gravid uterus, free intraperitoneal blood, solitary fibroid in right corner of fundus with ruptured subserosal vein	Myomectomy	Spontaneous abortion 2nd post-operative day recovered
			Posteriorly placed fibroid 7 cm. in diameter with ruptured superficial vein	Removal of tumor	Recovered
Yes	3 days	Extrauterine pregnancy	Two large-sized fibroids with free intraperitoneal bleeding from a subserosal vein overlying one of the fibroids	Supravaginal hysterectomy	Recovered
Yes	3 days		Free blood in peritoneal cavity, irregular uterine fibroid with bleeding from dilated subserosal vein	Supracervical hysterectomy, salpingo-oophorectomy	Recovered

Table I—Cont'd

Author	Age	Parity	Menstrual history	Previously known pelvic tumor	Preceding trauma	Severity of shock	Pelvic tumor palpable on admission	Time lapsed from onset of illness to operation
15. Shapira and Starr ¹⁵	50				Reaching upwards to a high shelf	Mild	Yes	Few hours
16. Johansson ¹⁶	57	0	Normal menopause at 55	No	None	Mild	No	18 hours
17. Wolfring ¹⁷	36	0	Eighth month of normal pregnancy			Moderate to severe	No	Few hours
18. Shelfo ¹⁸	52	ii	Normal		None	Severe	Yes	Few hours
19. Shelfo ¹⁸	44	i	Irregular periods preceding few months		None	None initially, severe shock third day after admission	Yes	1 day
20. Weidekamp ¹⁹	31	0	Normal		None	Severe	Yes	Few hours
21. Schneider and Jemerin ²⁰	40		Amenorrhea preceding 4 months, vaginal spotting preceding few days	Yes	None	Moderate	Yes	14 hours
22. Woodruff ²¹	38	ii	Irregular periods preceding 3 months		None	Moderate	Yes	Few hours
23. Hasskarl ⁶	38	iii	Onset of normal menstrual period preceding day		Onset of pain after gardening	Slight	Yes	Few hours
24. Li and Braden ²²	37	0	Normal menstrual bleeding a month previously	Yes	Onset of pain while riding in bus	Severe	Yes	Few hours
25. Kovacovics ²³	43	0	Onset of normal period 1 day previously	Yes	Fell and traumatized lower abdomen 2 days previously	Moderate	Yes	Few hours
26. Saidi and associates	34	i	Onset of normal cycle	No	None	Severe	No	2 hours

from a ruptured vessel at the stalk of a pedunculated and twisted fibroid; in others there was evidence of infarction or malig-

nant or aseptic degeneration of the tumor with secondary hemorrhage. This leaves 26 cases that we consider to be bona fide exam-

	Time lapse from onset of illness to operation	Preoperative diagnosis	Operative findings	Operation performed	Results
Yes	Few hours		Free intraperitoneal blood, lobulated fibroid with ruptured subserosal vein	Supravaginal hysterectomy and bilateral salpingectomy and oophorectomy	Recovered
No	18 hours	Torsion of cystic ovary	Single tumor the size of child's head on upper surface of uterus, enlarged varicose veins with bleeding from perforated site in vein	Supravaginal amputation of uterus	Recovered
No	Few hours	Acute appendicitis	Gravid uterus with extreme dilatation of subperitoneal veins of the fundus, free blood in peritoneal cavity	Cesarean section, supravaginal amputation of uterus	Recovered
Yes	Few hours	Intra-abdominal bleeding of undetermined site	Free blood in peritoneal cavity, solitary fibroid 7 by 5 cm. with ruptured superficial varicose vein	Supracervical hysterectomy	Recovered
Yes	3 days	Uterine fibroid with cervical compression symptom	Free blood in peritoneal cavity, multiple fibroids, ruptured large vein on upper pole of one of these	Total extirpation of uterine myoma	Recovered
Yes	Few hours	Rupture of vessel on fibroid	Free blood in peritoneal cavity, multiple fibroids, one 10 cm. with rupture on posterior surface	Fundectomy and myomectomy	Recovered
Yes	14 hours	Fibroid uterus, bleeding of undetermined site	About 2 L. of blood in peritoneal cavity, large fibroid uterus with defect in a posterior superficial vein	Supracervical hysterectomy	Recovered
Yes	Few hours	Ruptured ectopic pregnancy	3 pints of blood in peritoneal cavity, large posterior subperitoneal fibroid with rupture of enormous superficial vein	Subtotal hysterectomy	Recovered
Yes	Few hours	Acute abdominal emergency	Free blood in peritoneal cavity, multiple fibroids, a 10 cm. fibroid with corona of veins and rupture of one of these	Total hysterectomy	Recovered
Yes	Few hours	Ruptured ectopic pregnancy	1,500 c.c. free blood in peritoneal cavity, on anterior surface of large myoma a ruptured varix present, 1.5 cm. in diameter	Subtotal hysterectomy	Recovered
Yes	Few hours	Extrauterine pregnancy	1,000 c.c. free blood in peritoneal cavity large fibroid with rupture of subserosal vein overlying the tumor	Supravaginal extirpation of uterus	Recovered
No	2 hours	Ruptured ectopic pregnancy	Large quantities of free blood in peritoneal cavity from perforated subserous veins overlying subserosal fibroid	Myomectomy	Recovered

ples, bringing the total number in the world literature to 43.

Table I also shows that in the majority of

instances the menstrual cycle of the patient had recently become irregular, or the acute episode occurred at the onset of a normal

period. The persistence of the signs and symptoms of an intra-abdominal catastrophe in all patients necessitated emergency laparotomy but a correct preoperative diagnosis was made in only 3 cases.

Summary and conclusions

1. Massive intra-abdominal hemorrhage from subserous veins overlying a uterine fibroid, though rare, is a serious clinical entity. The degree of blood loss is life endangering and demands prompt surgical intervention.

2. The clinical picture is uniformly one

which demands prompt surgical exploration. Treatment by myomectomy is feasible and successful and is recommended when sacrifice of the uterus is undesirable.

3. Both trauma and increased vascular flow to pelvic organs during menstruation or pregnancy have been considered responsible for the onset of massive intra-abdominal bleeding in these cases. In our patient the possibility of a forceful peripheral migration of the fibroid is suggested.

4. A summary of 26 cases reported in the world since 1922 is presented, bringing the total number to 43.

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Ten years' experience with ovarian malignancy at a United States naval hospital

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MANAGEMENT of malignancy of the female genital tract has improved through recently developed techniques as witnessed by improved cure and survival figures in cancer of the cervix and to some extent in endometrial carcinoma. Unfortunately, little satisfaction can be taken in reviewing the end results of therapy in ovarian malignancy. Long known as the silent executioner, malignant ovarian neoplastic processes have continued to pursue their lethal way, claiming as their victims a relatively constant percentage of women each year, despite all of our cancer consciousness, education, and changing therapeutic procedures. It is distressing not to be able to make appreciable progress in solving the problem, and also to have the feeling that some of our best results come in cases where the ovarian diagnosis was unsuspected and resulted from an examination or operation for an unrelated complaint.

Material

This review includes all cases of ovarian malignancy which have been registered with the Gynecological Tumor Board of this hospital since its inception and have had any form of treatment. Eighty-one cases of primary ovarian malignancy are presented and these are summarized in Tables I to III. Ex-

cluded are 14 cases of metastatic disease of the ovary, a few cases that were found incidentally at postmortem examination for death from other causes, and cases that presented strong clinical evidence of ovarian malignancy but could not, for one reason or another, be proved histologically. Cases transferred from other institutions in which the diagnosis was made and partial therapy already started are included. Also included is the inevitable "lost to follow-up" category. In spite of a most energetic Tumor Board secretary, this latter group is larger than we would wish.

Satisfactory analysis of such a series should include the patient's age, duration of symptoms, the complete plan of treatment instituted, length of survival, or time elapsed from establishment of diagnosis to death. It should include management of cases with treatment started elsewhere, and procedures done in palliation of patients initially treated here or patients of other clinics presenting themselves for management of metastatic or recurrent disease. To attempt to reduce the series reported to groups fitting specifically into any one division, including histologic variety, clinical staging, all modalities of treatment given, and survival charted against pathology and staging would reduce each to a "not statistically significant" number.

The primary carcinomas have been divided into three groups: the predominantly solid, the cystic, and the dysontogenetic neoplasms. These have been divided into clini-

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The opinions expressed herein are those of the authors and do not necessarily reflect the views of the Department of the Navy.

cal Stages I to IV, by Munnell and Taylor's¹ classification: Stage I, confined to 1 ovary; Stage II, confined to both ovaries; Stage III, confined to pelvic organs and pelvic peritoneum; Stage IV, extrapelvic spread, including abdominal viscera, omentum, and/or more distant metastases. The lesions were staged as found at the time of first treatment.

The patients after treatment have been classified as alive without disease, alive with disease, dead, and lost to follow-up. Patients are considered lost to follow-up if they do not return to the Gynecology Tumor Board within 6 months after their last scheduled appointment or forward to the Tumor Board the results of evaluation at another Tumor Clinic or by their private physician. Fifteen patients are in this group, which is 13.5 per cent of the total number. This is high, even for the migrating service dependent type patients we treat, and is evidence for a more intensive patient education program and more vigorous social service support for the Tumor Board.

Results

Only 29 of the 81 patients were alive without disease at the time of the cut-off date of this study. Of these 16 have been followed for 5 or more years, 15 are without disease, and 1 presents evidence of remaining tumor. This represents a 19.8 per cent 5 year survival rate.

Six cases of multiple primary malignancy occurring in the same patient are included in the review. One patient who died of metastatic bilateral ovarian carcinoma in November, 1958, had a history of radical mastectomy in January, 1956, for adenocarcinoma of the right breast. In January, 1957, the left breast was removed because of intraductal cancer—the ovarian metastatic lesions were of this histologic pattern.

A patient who had a hysterectomy, a bilateral salpingo-oophorectomy, and external x-ray therapy for bilateral cystadenocarcinoma of the ovaries in 1948 had a vulvectomy for intraepithelial carcinoma of the left vulva in 1953. At that time, she had no

evidence of internal pelvic disease but was lost to follow-up shortly thereafter.

A patient who had a hysterectomy, a bilateral salpingo-oophorectomy, and cobalt⁶⁰ therapy for pseudomucinous cystadenocarcinoma of the right ovary was found to have a granulosa cell tumor in a grossly normal left ovary; she is without evidence of disease at 18 months.

A patient with anaplastic squamous cell cervical cancer presented apparently primary bilateral solid adenocarcinoma of the ovaries at postmortem examination.

Finally, 2 patients with carcinoma in situ of the cervix were found to have papillary serous cystadenocarcinoma of the left ovary and bilateral adenocarcinoma of the ovaries, respectively. Both of these patients were in their early forties and presented gross ovarian abnormalities at operation for hysterectomy. They are both living and without evidence of disease more than 5 years after treatment.

Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, intraperitoneal instillation of radioactive gold, followed by cobalt⁶⁰ or conventional deep x-ray treatment have been used in 24 of our cases. Of this number 6 are dead, 3 are alive with disease, and 15 are living from less than 1 to 5 or more years without evidence of recurrence.

Comment

Management of ovarian malignancy has two aspects, prophylactic and definitive. Prophylactically, we are becoming much more critical of the "enlarged ovary, probably within normal limits" and "indefinite sensation of fullness in the left adnexa" type of finding that is not infrequently reported, particularly if the patient is over 40 years of age. These patients are requested to return in 1 week instead of 3 to 6 months and are advised to cleanse the lower bowel before re-examination. If the indecision remains, staff consultation is requested and the patient is not released until the matter is settled. Our attitude toward laparotomy with wedge ovarian biopsy is broadening

with the feeling that it would be better judgment to perform an exploratory operation even if negative, than to allow an early malignancy to advance in clinical staging. The enthusiasm of the personnel of our clinic for culdoscopy has waxed and waned. At present, interest has been stimulated and it is felt this is a valuable diagnostic procedure in such cases.

Definitive treatment is considered from two standpoints, management directed toward cure and procedures done in palliation of advanced disease. All patients have the usual preoperative exclusion workup; chest, long bone, and skull x-ray studies, cystoscopy, and intravenous or retrograde pyelography, proctoscopy, and barium enema. Complete hemogram, with blood volume studies if indicated, is ordered and any concomitant medical condition is evaluated thoroughly. The curative program includes hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. If ascitic fluid is present, a sufficient amount is sent to the laboratory for cell block study; if the pelvis is relatively dry, lavage with 4 ounces of saline is performed and the washings are sent for cytology. A No. 15 polyethylene tube is inserted into the right or left of the midline incision and anchored firmly in place. Closure is routine except for the use of No. 30 wire interrupted fascial sutures. If there is any doubt about the presence of malignancy, salpingo-oophorectomy is done and the specimen is sent for frozen section. If the pathologist's report is equivocal, as frequently happens, and particularly if the patient is in a younger age group, nothing more is done. The remaining ovary is not wedge biopsied unless grossly abnormal. If the paraffin sections reveal malignancy, removal of the uterus, remaining adnexa, and omentum, and insertion of the polyethylene tube is done on the third or fourth postoperative day. Radioactive gold in doses of 100 to 150 mc., depending on the patient's weight and build, is inserted through the tube on the fourth postoperative day with about 400 ml. of vehicle. The patient is then placed on the rocking bed for a minimum of

Table I. Incidence, classification, stage, and gross results of cystic neoplasms

Pathologic diagnosis	Clinical stage				Total
	I	II	III	IV	
Serous cystadenocarcinoma	6	5	11	16	38
Pseudomucinous cystadenocarcinoma	5	1	3	2	11
Papillary cystadenocarcinoma	1	4	0	2	7
Total	12	10	14	20	56
Alive without disease	10	4	10	2	26
Alive with disease	0	0	0	6	6
Dead	1	2	2	10	15
Lost to follow-up	1	4	2	2	9

Table II. Incidence, classification, stage, and gross results of solid neoplasms

Pathologic diagnosis	Clinical stage				Total
	I	II	III	IV	
Adenocarcinoma	0	1	1	8	10
Undifferentiated	0	1	0	0	1
Teratocarcinoma	0	0	0	1	1
Teratoma with chondrosarcoma	0	0	0	1	1
Carcinoma*	0	0	0	3	3
Total	0	2	1	13	16
Alive without disease	0	1	0	0	1
Alive with disease	0	1	0	0	1
Dead	0	0	1	12	13
Lost to follow-up	0	0	0	1	1

*Diagnosis established elsewhere, not classified.

Table III. Incidence, classification, stage, and gross results of dysontogenetic neoplasms

Pathologic diagnosis	Clinical stage				Total
	I	II	III	IV	
Arrhenoblastoma	1	0	0	0	1
Granulosa cell	2	0	0	1	3
Dysgerminoma	2	2	0	1	5
Total	5	2	0	2	9
Alive without disease	3	0	0	0	3
Alive with disease	0	0	0	0	0
Dead	1	2	0	2	5
Lost to follow-up	1	0	0	0	1

4 hours and the abdomen is scanned 24 and 72 hours later. Teletherapy with cobalt⁶⁰ to deliver 4,000 rads to the lower abdomen and 2,500 rads to the upper abdomen is started from 10 to 14 days after operation and is usually completed in 4 to 5 weeks.

Palliative procedures are carried out in patients of 2 general classifications. The first is in those patients in whom the diagnosis has been established and recurrent disease of the pelvis and elsewhere is evident. Exclusion laboratory and x-ray studies are repeated and management is highly individualized. Cobalt⁶⁰ therapy is extended to full tolerance if the limit has not already been reached. Ascites is relieved and gold or nitrogen mustard instilled if feasible. If the palpable lesion presents any evidence of localization, laparotomy for a second look is done. Any tumor that can be removed is excised and, if indicated, the urinary tract and/or bowel are diverted. Our experience with chemical therapy is largely limited to the use of nitrogen mustard and thio-TEPA. The former is used either intraperitoneally or intravenously and the latter intravenously with the usual monitoring of the blood picture. When the unfortunate Stage IV patient is seen for the first time, an attempt

to remove the pelvic genital organs, the omentum, and as much of the tumor as possible, is made at the initial surgical procedure. If the extent of growth of the lesion makes this a manifest impossibility, biopsy, and polyethylene tube insertion only are done and the patient is given gold and external radiation therapy. Some satisfaction can be gained by seeing a few of these patients respond to the point where operation can be performed. Chemical therapeutic agents are also used as indicated in further palliation.

Experience has taught us to exercise caution in combining the radioactive intraperitoneal agent with external radiation and this was brought to our attention by the following case.

A 45-year-old white woman who had been recently treated in our clinic for chronic cervicitis was found to have rather suddenly developed a large pelvic mass and ascites. On July 29, 1958, at operation, bilateral carcinoma of the ovaries with general metastases was found. Hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed. The pathologic diagnosis was papillary serous cystadenocarcinoma of both ovaries with metastases to the tubes, pelvic peritoneum, and omentum. The pa-

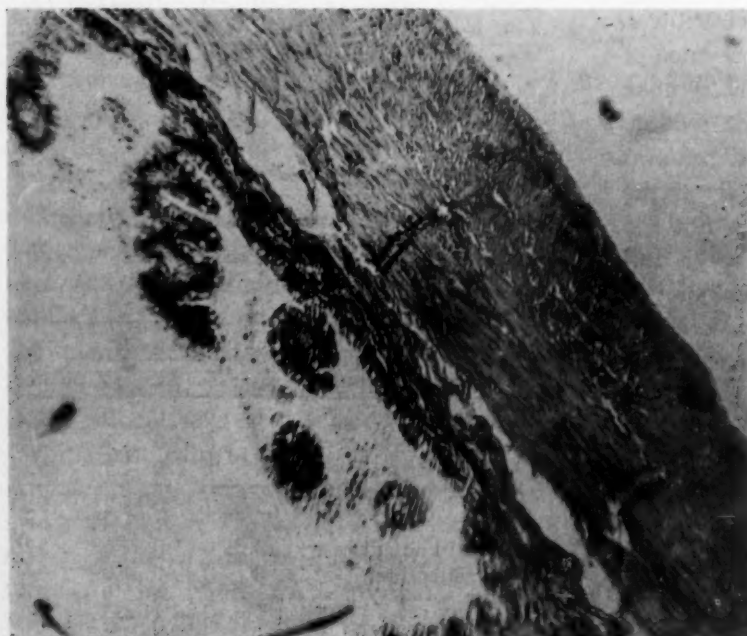


Fig. 1. Section of normal ileum from 44-year-old white woman. Relation of serosal layer to underlying circular muscle, longitudinal muscle, and mucosal layers is shown. ($\times 70$; reduced $\frac{1}{4}$.)

tient was given 10.4 mg. of nitrogen mustard intraperitoneally the day following the operation and on Aug. 10, 1958, 101.6 mc. of Au^{198} was instilled into the peritoneal cavity. Cobalt⁶⁰ therapy was started on Aug. 22, 1958, and over a period of 57 days 4,109 rads were delivered into the pelvis and lower periaortic nodes and 2,345 rads into the upper periaortic nodes. The patient, who had been in an extremely debilitated condition, showed some improvement and at Tumor Board follow-up visits on Nov. 3, 1958, and on Jan. 8, 1959, was noted to be feeling better, gaining weight, and presenting no palpable evidence of pelvic or abdominal disease. However, on Feb. 12, 1959, she was found to have massive ascites and 100.28 mc. of Au^{198} was instilled after paracentesis on Feb. 18, 1959. No appreciable effect on the ascites was noted; on April 2, 1959, repeat paracentesis was followed by the instillation of nitrogen mustard. The patient showed increasing debility and inanition and death occurred on June 1, 1959.

On postmortem examination an extreme fibrosis reaction including the pleurodiaphragmatic area, perisplenitis, and perihepatitis was found with marked enterectasis causing partial obstruction. The only evidence of carcinoma was some implants on the small intestine. Photomicrographs (Figs. 1 and 2) show the subserosal fibrotic lesion encountered, compared with normal ileum from a woman the same age as the patient.

It was felt that this patient actually died from faulty digestive function due to altered intestinal physiology secondary to the fibrosis, rather than from carcinoma. Reactions to a lesser degree have been noted in the intestinal tracts of 2 other patients who succumbed to advancing malignant processes. At present it is our policy not to repeat intraperitoneal Au^{198} but to treat recurring ascites with chemical agents.

This plan of management has evolved from a study of the literature and the experience gained in our clinic. The literature contains many plans of therapy, some quite different in procedure. For example, Munnell and associates² feel that improvement in therapeutic results follows better radiation techniques rather than an operation. Latour and Davis³ report better results with operation alone and doubt whether x-ray studies have a palliative effect in prolonging life. The question of prophylactic oophorectomy in the patient at or around 40 years of age is answered in the negative by Hollenbeck⁴ and in the affirmative by Counseller and co-workers.⁵ Honest, divergent opinions are numerous and are arrived at also by digesting the literature and the personal experience of the reporting clinic. Fortunately, the



Fig. 2. Section of ileum from patient. Marked fibrosis reaction of serosal layer overlying circular muscle fibers is shown. ($\times 70$; reduced $\frac{1}{4}$.)

over-all incidence of ovarian malignancy is so low that it is impossible for even the larger centers to accumulate enough cases to evaluate enough controlled plans of therapy to state categorically one plan is best. A series of more than 300 loses significance when we find it goes back 20 or more years and the clinic has passed through different policy eras regarding treatment.

Favorable results in any given case of ovarian cancer depend primarily on starting surgical treatment while the neoplasm is in clinical Stage I. Adjunctive treatment to improve results must be standardized to rule in or out the several approaches and find out what combination of procedures, modalities, or chemical agents give the best results.

In this study we encountered tumors that were identical in histology, staging, and treatment; yet one patient would survive for 5 years and her counterpart would be dead of metastases in 6 months. Transportation of malignant cells at the time of operation has been conclusively demonstrated.⁶ Is the matter of patient response entirely one of differing host resistance or is there a quantitative reaction to the tumor cell shower at operation? Should intravenous chemotherapeutic agents be given during and immediately after operative procedures? The answer must come from the combined experience of many clinics.

If improvement is to be obtained, the matter is one of education; first, of the public as to the necessity of periodic pelvic examinations and, second, of the profession to pool results of all clinics, to standardize reporting, therapeutic measures used, and year-by-year survival figures.

Summary

1. Eighty-one cases of primary ovarian tumors have been presented.

2. Of the primary tumors, 46.9 per cent were serous cystadenocarcinomas. Pseudomucinous cystadenocarcinoma, 13.6 per cent, and adenocarcinoma, 12.3 per cent, were next in the order of frequency of occurrence.

3. Of the patients alive without disease from less than 1 year to more than 5 years, 13 out of 17 had Stage I lesions, 5 out of 14 Stage II, 10 out of 15 Stage III, and 2 out of 35 Stage IV.

4. Our over-all 5 year survival rate is 19.8 per cent.

5. Patients alive without disease in other than Stage I are limited to the cystic group. Of the 17 in this category, 11 had serous cystadenocarcinoma and 6 had pseudomucinous cystadenocarcinoma. Inasmuch as the serous type of the lesion occurred almost three and one-half times as frequently as the pseudomucinous, the percentage indicates that the latter showed the better response to therapy.

6. Thirteen and one-half per cent of our patients have been lost to follow-up.

7. Six cases of multiple primary malignancy, of which one was ovarian, occurred in the series, and are briefly presented.

8. Management of ovarian malignancy in this clinic has been outlined. The necessity of caution when combining intraperitoneal radioactive gold, Au¹⁹⁸, with external radiation is emphasized.

Conclusion

With present methods of therapy improvement apparently will come only by increasing the percentage of diagnoses of Stage I ovarian neoplasms. Increasing numbers of women are accepting periodic cytologic studies for the detection of cervical cancer; critical adnexal evaluation should be an important part of this examination.

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Unusual teratoma of the ovary with implantation in the abdominal cavity

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THERE have been numerous publications on teratomas of the ovary including reviews by Ackerman,¹ Anderson,² Boyd,³ Blackwell,⁴ Ewing,⁵ and Willis.⁶ We wish to report a case of a large teratoma which occurred in a female infant and produced unusual implants in the abdominal cavity.

Case report

A 22-month-old female infant was admitted to the White Memorial Hospital on April 4, 1958, because of abdominal enlargement and cachexia. The infant had been well until 7 months before admission when she developed a temperature of 104° F. and gradual abdominal distention over the ensuing months. The first exploratory laparotomy was performed at the age of 16 months in another hospital. A biopsy of the abdominal tumor was reported to be consistent with a neuroblastoma. The tumor was not removed at that time, and there had been no further enlargement of the abdomen since. Birth, development, and family history were not contributory.

Physical examination revealed an irritable, emaciated female infant who appeared quite weak. A large tumor occupying almost the entire peritoneal cavity was noted. The abdomen measured 64 cm. in circumference at the navel and 72 cm. at a level between the navel and the xyphoid process of the sternum. The superficial veins were prominent and extended upward to the chest. The liver edge was not palpable. The temperature was 99.2° F.; pulse rate, 120; and

respirations, 40. The urine contained 10 to 15 pus cells per high-power field. The hemoglobin level was 12.5 Gm. per 100 ml.; hematocrit determination, 42 per cent; and white cell count, 8,100 with 58 per cent neutrophils, 30 per cent lymphocytes, 2 per cent monocytes, 6 per cent eosinophils, and 4 per cent basophils. Findings on bone marrow study were essentially normal. The frontooccipital circumference of the head was 48 cm., and a skull x-ray showed no abnormality. A second abdominal exploration was performed on April 16, 1958.

A cystic mass with 3 L. of fluid which contained pieces of floating fatty substance resembling sebaceous material was found in the abdomen. The mass was encapsulated and adherent to most of its surroundings. The cyst was completely intraperitoneal. The stomach was adherent to the dome of the cyst and was dissected free. The pedicle of the tumor was found in the left broad ligament. The mass was also adherent on the inferior surface of the left diaphragm. The liver was smooth and pale in color, the gall bladder was filled with green bile, and the appendix was grossly normal. The right tube measured 8 cm., and along its inferior border was an ovary measuring 4 by 3 by 2 cm. The uterus was identified. The patient was discharged from the hospital on April 23. Follow-up study 2 years later showed no evidence of recurrence of the tumor.

Gross examination. Specimen 1 consisted of a cystic mass measuring 20 by 15 by 11 cm. The serosal surface was pinkish gray, smooth, and glistening, and showed small injected vessels and areas of adhesions. In one area a grayish white, irregular, firm mass protruded through the capsule. Section showed a cystic mass containing dark brown serous fluid with numerous

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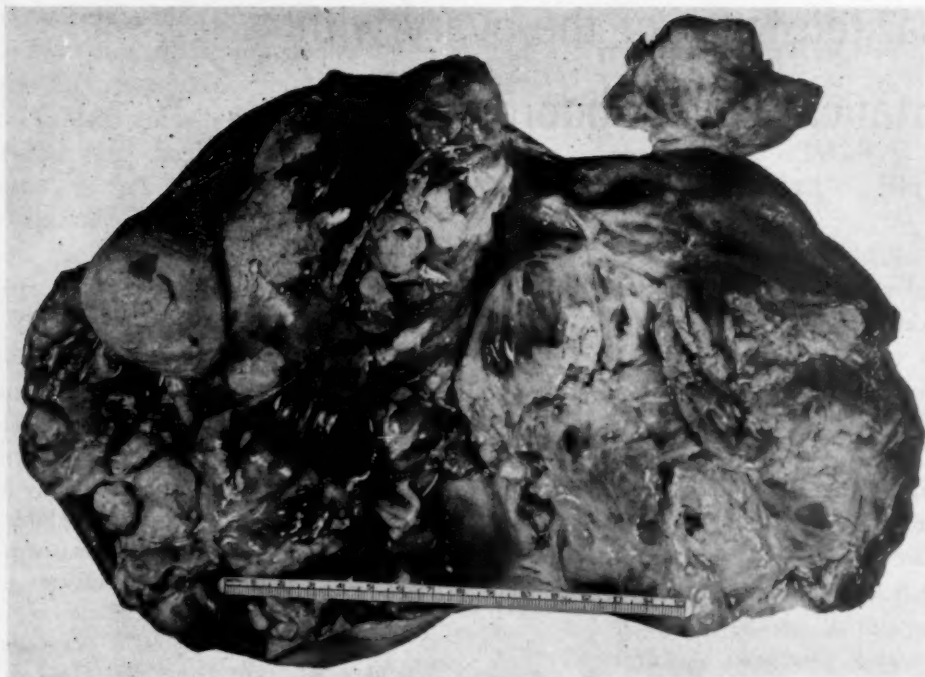


Fig. 1. Bisected main abdominal tumor mass showing various sized teratomatous nodules. In the upper right corner is an irregular mass removed from the inferior surface of the dome of the diaphragm.

yellow fatty particles. There were various sized, irregularly shaped, pinkish gray, slimy, soft tumor masses. Sections of these tumors showed numerous minute secondary cysts containing mucin, bony fragments, cartilaginous tissue, and grayish white firm nodules with dark hair and dark brown degenerated material. Some areas were covered with a bright yellow pasty material (Fig. 1).

Specimen 2 consisted of a portion of the omentum measuring 15 by 10 cm. The surface showed numerous small, grayish white, firm nodules measuring 0.2 to 0.3 cm. in diameter.

Specimen 3 consisted of a grayish white slimy tumor mass measuring 5 by 4 by 2 cm. stated to be from the inferior surface of the dome of the diaphragm. Section showed pinkish gray soft tissue with numerous minor cysts and bright yellow substances.

Microscopy examination. Multiple sections of the main tumor mass revealed a variety of tissues from all three germ layers, including elements of normal appearing glial tissue, hair follicles, epidermal inclusion cysts filled with keratinous desquamated material, bronchial mucosa, hyaline cartilage, skin, and adnexal structures such as sebaceous glands and sudoriferous glands (Fig. 2). The Fallopian tube was sur-

rounded by adult dermoid tissue. The sex chromosome pattern of the tumor was female.

The tissue obtained from the diaphragm showed the same multiplicity of normal adult tissues in a chaotic arrangement as was encountered in the ovarian tumor. Multiple sections showed no evidence of malignancy. The pathological diagnosis was benign teratoma of the left ovary with widespread dispersion of the contents, probably due to implantation from spillage.

Microscopy examination of the firm nodules from the omentum showed glial tissue without admixture of the teratomatous tissue found in the main tumor mass. Special staining with Holzer stain confirmed the presence of astrocytes (Fig. 3).

Comment

This case presents several points of interest. The age of the patient, 16 months when first seen, is younger than ages in previously reported cases. Dermoid cysts are rare in infancy. Blackwell⁴ studied 225 patients who had cystic teratomas removed surgically at the Mayo Clinic. The youngest patient in this group was 7 years old and the oldest,

72 years old. Shattock⁷ reported a case of dermoid cyst of the ovary in a 2½-year-old child. Doran⁸ reported 3 cases in children, 22 months, 2 years, and 2 years and 11 months of age. The malignant transformation of benign cystic teratomas of the ovary occurred at an average age of 45.4 years in a study by Peterson⁹ and the youngest patient in his study was 9 years old.

Another point of interest in this case is the exceptionally large size of the tumor in relation to the size of the patient. Blackwell⁴ found the mean size of the dermoid cyst to be 8 cm. in diameter. The largest tumor of his series in all age groups measured 30 cm.; however, the largest in the 7 to 10 age group (3 cases) measured 15 cm. in the greatest

diameter. Shattock's⁷ case in a 2½-year-old child was reported to consist solely of a hydrocephalic head with brain measuring 5.5 by 3 cm. in the greatest diameter.

The most interesting and unusual aspect of this case is the widespread implantation of the teratomatous tissue, presumably as a result of spillage following the earlier biopsy. The capsule of the dermoid cyst showed a line of scar on the surface with protrusion of granular tissue. Examination by multiple microscopy sections failed to show evidence of malignancy. Quer and associates¹⁰ reported a case of a ruptured dermoid cyst giving a clinical picture of carcinomatosis. Upon opening of the abdominal cavity in his case, marked adhesions

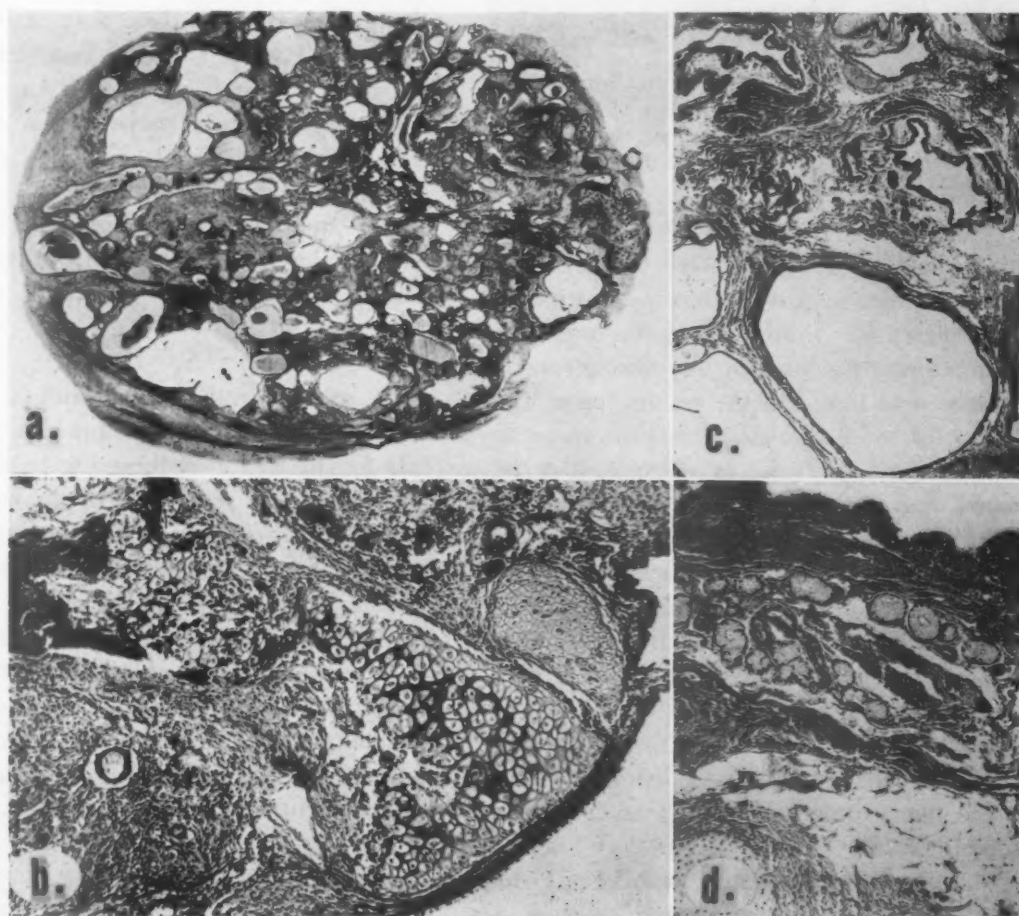


Fig. 2. *a*, Entire microsection of one of the secondary nodules shown in Fig. 1. ($\times 6$; reduced $\frac{1}{3}$.) *b*, Enlargement of a portion of *a* showing cartilaginous and osteoid tissues. ($\times 100$; reduced $\frac{1}{3}$.) *c*, Microsection of the tumor from the diaphragm showing muscle fibers and cysts. ($\times 100$; reduced $\frac{1}{3}$.) *d*, Microsection of the tumor from the diaphragm showing bronchial epithelium and mucus secreting glands. ($\times 100$; reduced $\frac{1}{3}$.)

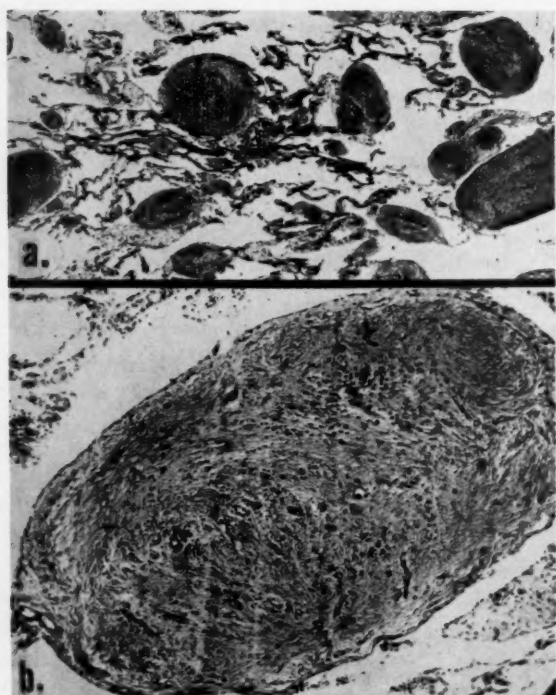


Fig. 3. *a*, Microsection showing the firm nodules of glial tissue in the areolar spaces of the omentum. (Hematoxylin and eosin. $\times 6$; reduced $\frac{1}{3}$.) *b*, Enlargement of one of the nodules shown in *a*, ($\times 100$; reduced $\frac{1}{3}$.)

and a patchy, oily fluid were noted on the serosa. Extensive granulomas with presence of foreign body giant cells were found on microscopy examination. No foreign body reaction was found in the present case. The finding of isolated nodules of glial tissue in the omentum, in view of the mixed ecto-, meso-, and endodermal composition of the main tumor, is unexpected. It is difficult to understand why only the differentiated glial cells showed the potentiality to "metastasize" to the omentum. No previous report of a case of "benign omental metastasis" of glial tissue has been found in the literature.

The masses in the dome of the diaphragm were found to be a mixture identical to that in the main tumor. This probably indicates that these masses may have been caused by implantation, but the nodules in the omentum must have originated through a different mechanism. The tumor masses on the inferior surface of the diaphragm are located near the cardia of the stomach and may be the logical source of retrograde

spread to the omentum through the lymphatic backflow of isolated single cells and small cell masses. Omental metastasis is commonly seen in cases of carcinoma of the stomach. Microscopically, small nodules of glial cells were seen in the lymphatic capillaries of the omentum but not in venous channels. The phenomenon is a well known fact, namely, glial tumors do not have the capacity to invade venous channels and, therefore, do not leave the cranial cavity to be the cause of widespread metastasis; but, if transplanted into subcutaneous tissue, for example, the tumorous tissue will grow, as shown by Zimmerman.^{11, 12}

Since a fairly large portion of the tumor from the dome of the diaphragm is composed of glial tissue, the chance of transplanted glial cells' surviving on the omentum is possibly greater than that of other cells. However, in view of the complete absence of other types of cells, one can speculate that the omentum may have a special affinity for the glial cells. This probably merits further investigation, since metastasis of brain tumors to other parts of the body is not known for reasons shown by Zimmerman.^{11, 12}

Summary

A case of a benign teratoma (dermoid cyst) of the ovary occurring in a 16-month-old female infant—believed to be the youngest patient on record with this condition—is reported. The size of this teratoma is unusual, and it is probably the largest one found in an infant of this age. This case also presents an unusual abdominal carcinomatosis-like spread of the benign teratoid tissue, and the omental implantations of "metastasizing" glial tissue is even more remarkable. The pathogenesis of this process warrants further investigation.

We are indebted to Clarence E. Stafford, M.D., Chairman and Professor, Department of Surgery, College of Medical Evangelists, for making available the clinical data for this case, and to Mr. Ed. Hamilton for the photographs.

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Hilus cell tumors of ovary

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OVARIAN hilus cell hyperplasia and tumors have been generally classified as masculinizing processes of the ovary along with arrhenoblastoma, adrenal cell rests, and luteomas.

The hilar cell processes have been of recent interest. The principal cell has been called hilus cell, sympathicotropic cell, ovarian Leydig or interstitial cell, and extraglandular Leydig cell. Berger² suggested the name "sympathicotropic cell" because of the apparent close connection with sympathetic nerve terminals. Taliaferro and associates⁷ described such a relationship in a case of hilus cell hyperplasia in 1953. The hilar cell of the ovary is similar in appearance to the interstitial testicular cell of Leydig in being ovoid, granular, and eosinophilic of variable size with an eccentric reticular nucleus commonly demonstrating a nucleolus. Specific cytoplasmic inclusion bodies (Reinke crystalloids) are commonly present in testicular Leydig cells and are frequently present in normal ovarian hilus cells.

Hilus cell hyperplasia and tumor both are unencapsulated proliferations wherein the hyperplasia is characterized by multiple associated but apparently unconnected small islands in contrast to the single larger mass of hilus cell tumor. Hyperplasia occurs more commonly bilaterally while hilus cell tumors have been usually reported unilaterally.

All except one case of hilus cell tumor

have been in women of the age range 46 to 54. Each was menopausal except one.

Young,⁹ in 1951, reviewed a case of marked hirsutism occurring and progressing during pregnancy in a 27-year-old woman. The hirsutism dramatically resolved following removal of a 5 by 8 cm. ovarian tumor diagnosed as a Leydig cell tumor. Berger, in 1942, reported a 50-year-old premenopausal woman with masculinizing changes which regressed after removal of a 0.5 cm. unilateral hilus cell tumor of the ovary. Reinke crystals were absent. No endocrine studies were reported. Sternberg⁶ reported 2 cases associated with masculinization, those of a 64-year-old woman with a 1.0 cm. unilateral ovarian tumor and an 86-year-old woman with bilateral ovarian tumors measuring 1.0 and 1.2 cm. Tissue from both patients revealed Reinke crystals. 17-Ketosteroid determinations were normal in each patient. In 1951, Sachs and Spiro⁵ described a 1.8 cm. ovarian tumor found at autopsy in a 47-year-old hypertensive woman with virilization. 17-Ketosteroid determinations were normal. The removal of an ovary nearly replaced by hilus cell tumor resulted in striking clinical improvement of masculinizing changes in a 46-year-old woman as reported by Waugh, Venning, and McEachern⁸ in 1949. 17-Ketosteroids were reported to be increased. The tissue revealed Reinke crystalloids. Berkheiser³ reported a 2.0 cm. ovarian hilus cell tumor in a 50-year-old hypertensive patient. Reinke crystalloids were absent.

Cases of hilus cell hyperplasia with masculinization have been reported by Sternberg (2 cases) in 1949, Taliaferro and asso-

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ciates⁷ in 1953, wherein the process was bilateral, and by Langley⁴ (2 cases) in 1954.

Case report

A. V., a 30-year-old woman, entered the hospital on Dec. 4, 1958, at 2 A.M., in active labor at term.

Previous history. Medicosurgical history was noncontributory except for an appendectomy in 1942. Obstetric history revealed term delivery of an 8 pound, 5 ounce infant following an 8 hour labor in 1951 and a 10 pound, 5 ounce infant in 1952 following an 11 hour labor. No complications occurred. A pregnancy in 1956 ended in a spontaneous abortion.

Menstrual history. Menarche occurred at age 10 with a cycle of 6 to 7 months with a moderate crampy flow of 5 to 6 days' duration. Intermittent, undefined, oral therapy had been administered for the menstrual irregularity. No menstrual period had occurred since the abortion in 1956.

Present admission. The present pregnancy was attended by a weight gain of 36 pounds from a usual weight of 170 pounds. No signs or symptoms of toxemia were noted and no bleeding had occurred. Minimal ankle edema was noted during the last trimester.

Physical examination revealed hirsutism manifest by increased facial and body hair with male distribution and character.

Eyes, ears, nose, and throat were without defect. The chest was clear to percussion and auscultation. The breasts were gravid pendulous. Heart tones were normal and no cardiomegaly

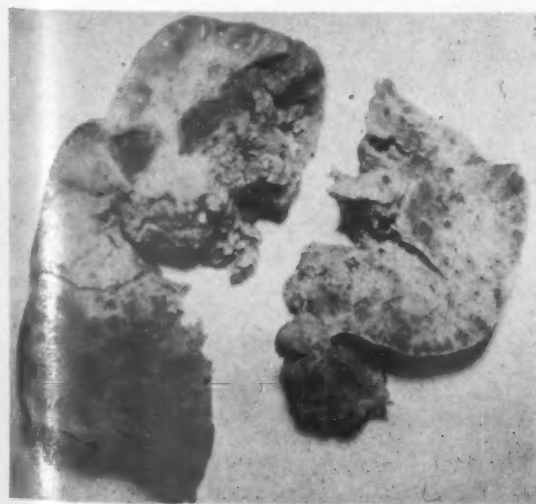


Fig. 1. Gross hemisected ovarian mass.

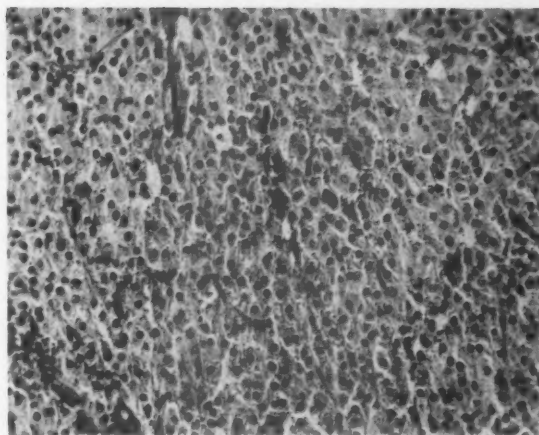


Fig. 2. Microscopic pattern of ovarian tumor. ($\times 300$; reduced $\frac{3}{4}$.)

was demonstrated. The abdomen was markedly pendulous and term pregnancy was evident. Strong uterine contractions occurred every 3 to 4 minutes, lasting 30 to 40 seconds. Fetal heart tones were within the left lower quadrant, 140 per minute. No masses were noted in the uterine wall or adnexa. Rectal examination revealed left occipitotransverse cephalic presentation at minus-3 station. With abdominal pressure a minus-1 station could be attained. Cervical dilatation was 2 to 3 cm. with 75 per cent effacement. Minimal ankle edema was present.

Laboratory results. The serologic test for syphilis was negative. The hemoglobin level was 10 Gm. per cent with a red cell count of 3.5 million. Oral glucose tolerance test revealed a fasting blood sugar level of 85 mg. per cent and levels of 155 mg. per cent at one-half hour, 190 mg. per cent at 1 hour, 158 mg. per cent at 2 hours, and 109 mg. per cent at 3 hours. Urinary sugar levels at 1, 2, and 3 hours were normal.

Hospital course. Delivery did not progress despite good uterine contractions. At 3 P.M. on Dec. 4, 1958, the patient was seen by a consultant who suggested a conservative approach at that time. Pelvimetry revealed no cephalopelvic disproportion. At 10:15 P.M. no progress had occurred. Contractions were diminished, appearing every 10 to 12 minutes, of poor quality. Examination revealed no alteration of station, cervical dilatation, or effacement. No adnexal masses could be determined. The patient was given morphine and rested until 8:30 A.M. on December 5 when ineffective irregular uterine contractions were noted. Labor did not progress. Fetal heart tones continued

of good quality. At 5 P.M., under spinal anesthesia, a cesarean section was performed with delivery of a 9 pound, 14 ounce living male. A right ovarian mass was then removed.

Gross pathology. The slightly bosselated, gray-tan, solid ovarian tumor exhibited a smooth surface and measured 8 by 5 by 4 cm. in greatest dimension. Sectioning revealed a pinkish tan to dark tan mottled surface with areas of hemorrhagic extravasation. No cystic areas were present within the tumor mass. A partial peripheral ring of residual cystic ovarian tissue was present, measuring up to 0.6 cm. in thickness.

Microscopic pathology. Hematoxylin and eosin sections revealed a cellular tumor composed of solid sheets of uniform cells with regular round, eccentrically placed nuclei, most of which contained a nucleolus. Abundant eosinophilic, slightly granular cytoplasm was present. The cells rested on a very vascular but scanty stroma. Reinke crystalloids could not be detected with certainty, even with use of Masson's trichrome stain.¹ Fat and periodic acid-Schiff stains were negative.

Comment

Unfortunately, this patient was lost to follow-up and alterations of secondary sexual characteristics could not be recorded. Although not demonstrated in this case, when present, Reinke crystals would aid substantially in differentiating the unencapsulated hilus cell tumor from the usually encapsulated arrhenoblastoma and adrenal cell rest tumor in the ovary. In addition, normal 17-ketosteroids in hirsute patients with an ovarian tumor might suggest a hilus cell tumor rather than arrhenoblastoma or adrenal cell rest tumor wherein the 17-ketosteroids are not uncommonly elevated.

Summary

The report of a hilus cell tumor of the ovary occurring during pregnancy is added to the literature.

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Bilateral Brenner tumors

Report of 2 cases

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IN 1907 Brenner described the tumor which now bears his name.¹ This tumor occurs rarely and is of particular interest when malignant or bilateral.

On careful review of the literature 20 reports²⁻⁹ describing bilateral Brenner tumors have been found, 2 of which^{3,7} have been overlooked in recent reviews. The present cases are the twenty-first and twenty-second to be reported.

Brenner tumors produce no characteristic symptoms and are usually benign and slow growing. The majority are found in women past the age of 50. Seventy per cent of these tumors are solid and approximately 30 per cent are found in the wall of a cyst which is usually a pseudomucinous cystadenoma. For many years it has been thought that they originated from "Walthard cell rests," but Greene¹⁰ has shown that Brenner tumors may arise from the ovarian stroma, the ovarian epithelium, and the rete ovarii. At the present time the total number of reported unilateral cases is probably over 300.¹¹ There have been 11 reports of malignant Brenner tumors.¹²

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Case 1. M. M., a 49-year-old gravida i, para i, entered the Mary Hitchcock Memorial Hospital complaining of intermittent right lower quadrant pain most severe in the midmenstrual cycle. The menstrual history was not remarkable. On physical examination a firm, slightly irregular mass was palpated suprapubically which by pelvic examination was thought to represent a myomatous uterus the size of a 12 to 14 weeks' pregnancy. No adnexal masses were palpated.

The hemoglobin level was 14.8 Gm.; erythrocyte sedimentation rate was 4 mm. per hour. An upper gastrointestinal series, cholecystogram, and intravenous pyelogram were all normal.

On Nov. 19, 1959, the patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and incidental appendectomy. Approximately 75 c.c. of clear serous fluid was noted in the peritoneal cavity. The uterus was enlarged and contained several intramural myomas. The ovaries were not remarkable. The abdominal organs including liver, gall bladder, spleen, stomach, and both kidneys were normal to palpation.

Pathologic examination of the uterus revealed 2 subserosal leiomyomas measuring 9.0 by 4.0 cm. in greatest dimension. These were on the anterosuperior surface and markedly distorted the uterine outline. The cervix, endometrium, and Fallopian tubes were not remarkable. The left ovary contained a firm, white, well circumscribed nodule 2.0 by 1.5 by 0.5 cm. which compressed its otherwise normal stroma. This nodule cut with a gritty sensation to reveal a non-bulging gray-white surface composed of interlacing tissue bundles. The right ovary contained

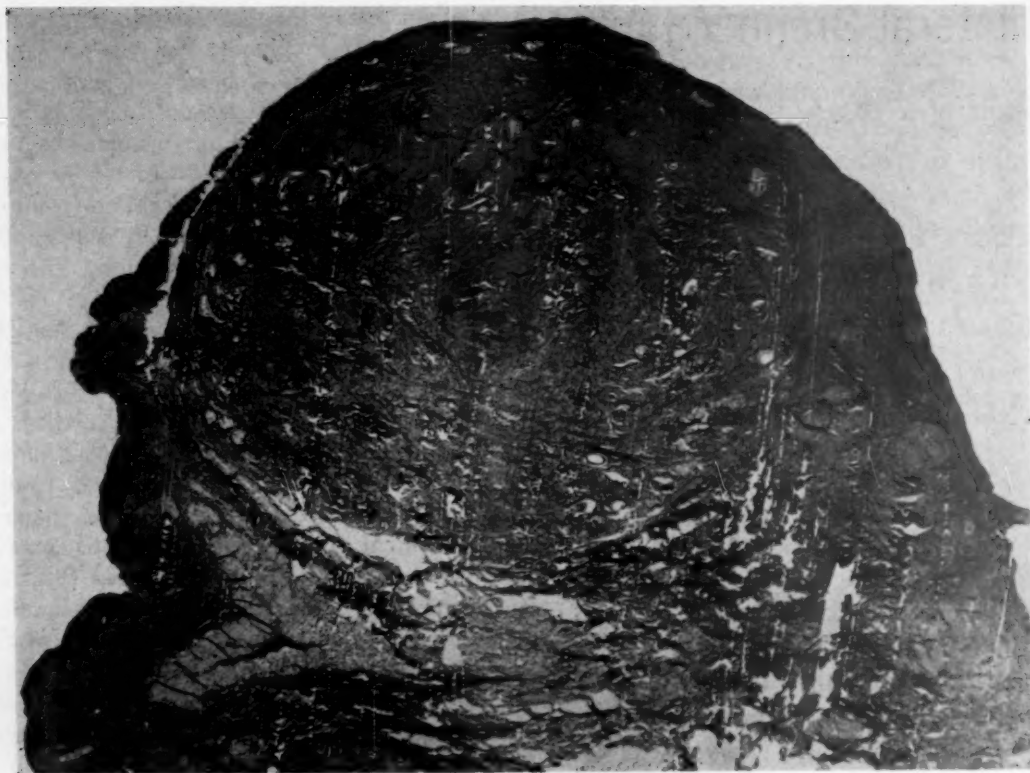


Fig. 1. Case 1. Clearly outlined 0.5 cm. Brenner tumor in right ovary. (Hematoxylin and eosin; $\times 20$.)

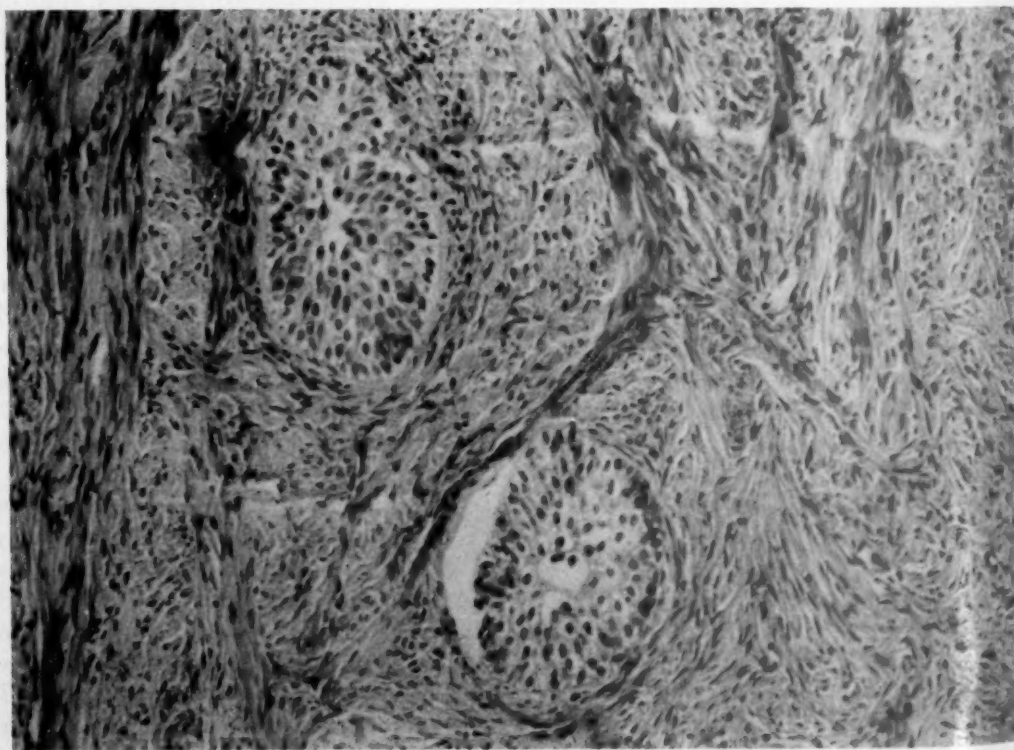


Fig. 2. Case 2. Dense fibrous tissue background of Brenner tumor with two nests of epithelial cells. (Hematoxylin and eosin; $\times 310$.)

a similar nodule 0.5 cm. in diameter (Fig. 1). Grossly these were thought to represent either fibromas or possibly Brenner tumors.

Microscopically both were typical Brenner tumors composed primarily of a dense fibrous tissue background in which there were numerous small, round, or oval nests of epithelial cells. These cells were all fairly large and uniform with small central nuclei and a pale cytoplasm. Often these nests of cells showed central degeneration which left a small cavity in the middle. No mucoid changes of the cells were present.

It was felt that the uterine leiomyomas accounted for this patient's symptoms and that the bilateral Brenner tumors were simply incidental findings. The patient had a benign postoperative course and has remained free of symptoms.

Case 2. B. T., a 65-year-old gravida ii, para ii, was admitted to the Mary Hitchcock Memorial Hospital with a history of four episodes of right upper quadrant pain associated with nausea and vomiting occurring during the preceding 6 months. Two of these episodes were associated with transient bouts of jaundice. The patient was approximately 15 years postmenopausal and had no gynecologic complaints. On physical examination she was noted to have icteric skin and sclera. Abdominally there was an enlarged tender liver and on pelvic examination the uterus was noted to be midline, anterior, and normal in size. The right adnexa was not well palpated but on the left there was a freely movable, nodular, firm mass approximately 8 to 10 cm. in size.

The hemoglobin level was 10.8 Gm. The erythrocyte sedimentation rate was 85 mm. per hour. The icteric index was 18 units. Results of a scout film of the abdomen, an upper gastrointestinal series, and a barium enema were all normal. A cholecystogram showed a nonfunctioning gall bladder with no opaque stones.

On May 24, 1951, an exploratory laparotomy was performed. The gall bladder and common duct contained numerous stones, and the pelvic mass previously described was found to be a hard but movable gray-yellow 8 cm. left ovarian mass. The right ovary had a similar appearance

but was about 4 cm. in its greatest diameter. Cholecystectomy, choledochostomy, and bilateral salpingo-oophorectomy were performed.

On pathologic examination the right ovary contained a 2.5 by 2.0 cm. firm, gray-yellow well-circumscribed nodule. A similar nodule, 7.0 by 6.5 cm. almost completely replaced the left ovary (Fig. 2).

Microscopically both were typical Brenner tumors and were similar in description to those in Case 1. It was felt that all of the patient's symptoms arose from gall bladder disease and that the pelvic pathology was an incidental finding. The patient did well postoperatively and was discharged from the hospital with a normal serum bilirubin level.

Summary

The twenty-first and twenty-second reported cases of bilateral Brenner tumors are presented.

We would like to thank Dr. George Lord for permission to report the second case.

Addendum. Since this paper was submitted for publication there have appeared two articles^{13, 14} reporting 3 new cases of bilateral Brenner tumors and 7 additional cases culled from the world literature.¹⁵⁻¹⁹ Three cases reported by Reagan²⁰ are not included in the above since he mentions that his specimens "were submitted to his institution from other sources"^{13, 20} and they may have been recorded elsewhere in the literature. Also a case of malignant Brenner tumor found in both ovaries, as reported by Rawson and Helman, has been excluded from the present series since we felt that the tumor involved the second ovary "by metastasis or invasion."²¹

The 4 cases of Reagan and Rawson and Helman were included in a recent review tabulating the number of cases of bilateral Brenner tumors. They have been excluded here.

We conclude that there are at least 32 cases of bilateral Brenner tumors reported in the literature, the present cases representing the thirty-first and thirty-second.

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Primary carcinoma in situ of the vagina

A case report and review of the literature

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IF PRIMARY cancer of the vagina can be diagnosed and treated while it is still intraepithelial, the cure rate should approach that of carcinoma in situ of the cervix. Unfortunately, the diagnosis of primary carcinoma of the vagina in the intraepithelial stage is rarely reported. None of the large series found in the literature reported any case of primary in situ carcinoma of the vagina.¹⁻⁷ The only mention found in the literature of this entity was made by Payne in the discussion following an article by Smith.⁸ He cited 2 cases. One patient was treated by partial vaginectomy and another by vaginal bomb irradiation. Both were alive after 4 years.

Primary invasive carcinoma of the vagina is a disease of rare occurrence, late diagnosis, and usually poor prognosis. The incidence quoted by most writers is approximately 2 per cent of genital malignancies in the female.⁹ The occurrence in Jews and Negroes is rare. The cause of this condition is unknown.

The late diagnosis of this condition is due to the following factors: (1) rapid growth and early extension of the tumor; (2) the mild, painless bleeding and leukorrhea that are generally the first symptoms are usually not present until the lesion is well advanced; (3) the location of this lesion is most often

in the upper third of the vagina in one of the fornices and, therefore, may be missed in the speculum examination where the cervix is usually the object of attention.

Because of these factors, the disease is often advanced before treatment can be initiated and, hence, offers a poor prognosis. Another cause of poor prognosis is the rich lymphatic drainage and the thin wall of the vagina which contribute to early spread and metastasis.

Our main purpose in reporting this case is to emphasize the part that can be played by vaginal cytology in making the diagnosis in the early stages as well as presenting the only documented case of primary intraepithelial carcinoma of the vagina.

Case report

Mrs. C. F., a 65-year-old white woman, gravida vi, para iv, who had had 2 abortions, was seen in the gynecology clinic at Touro Infirmary on June 11, 1956, with a complaint of mild vaginal bleeding of 2 days' duration. This was the first episode of vaginal bleeding since 1936, when menopause was induced by radium therapy because of severe chronic cervicitis proved by a previous biopsy. The history was otherwise noncontributory.

Pelvic examination revealed a small area of ulceration in the anterior vaginal fornix. The cervix was small and clean, and the uterus and ovaries were atrophic. Vaginal cytology revealed the presence of malignant cells suggestive of intraepithelial squamous cell carcinoma.

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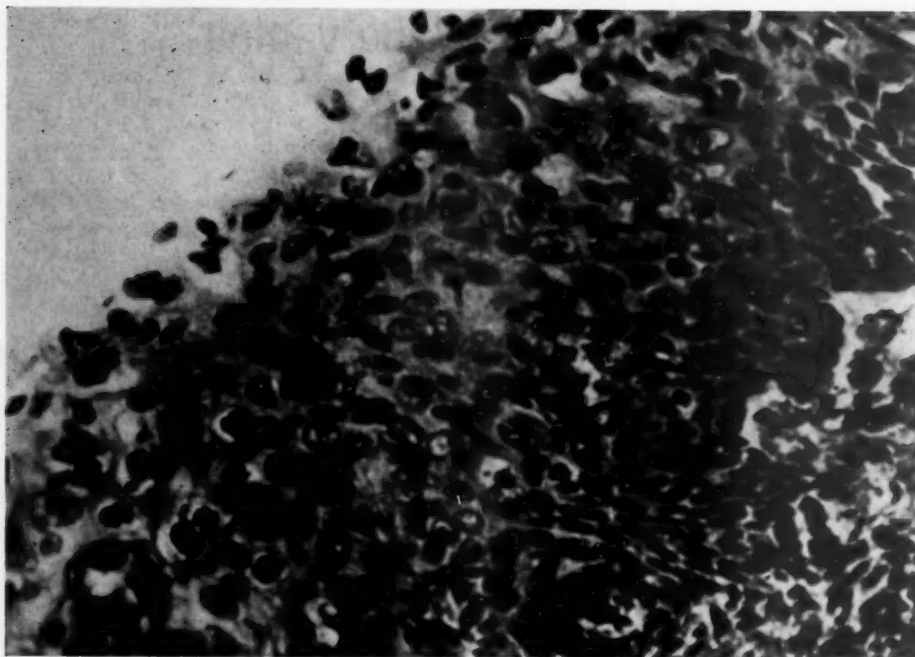


Fig. 1. Vaginal mucosa from partial vaginectomy performed June 21, 1956. The section shows epithelial pleomorphism and atypicalities with loss of polarity but without invasion.

She was admitted to the hospital for cervical and vaginal biopsy and uterine curettage, but the cervical canal was obliterated and flush with the vaginal wall. Therefore, only the vaginal biopsy could be done. The microscopic diagnosis of the vaginal biopsy submitted was "carcinoma in situ." Chest roentgenogram, electrocardiogram, barium enema, intravenous pyelogram, complete blood count, fasting blood sugar and nonprotein nitrogen levels, and urinalysis and serology findings were within normal limits.

She underwent a total hysterectomy, bilateral salpingo-oophorectomy, and an excision of the upper one third of the vagina on June 21, 1956. All tissues removed were free of malignancy except for an area of carcinoma in situ of the vagina not adjacent to the cervix (Fig. 1). She had an uncomplicated postoperative course and was seen in the postoperative clinic on five occasions between July, 1956, and September, 1958. At every visit, the vagina was described as "clean," with no areas of ulceration or erosion noted. However, no cytologic studies on the vaginal secretions were performed.

She returned to the gynecology clinic on Oct. 6, 1958 (26 months postoperatively) because of a bloody discharge and persisting right lower quadrant pain. Visualization of the vagina revealed multiple white, milium lesions on the vaginal cuff that oozed blood when traumatized.

Cytologic studies at that time revealed "probable squamous cell carcinoma." She was again admitted to the hospital and all laboratory findings and roentgenograms were essentially within normal limits.

A 2 by 3 cm. area of the vagina containing the lesions was excised. The histologic diagnosis was multiple foci of squamous cell carcinoma in situ of the vagina (Fig. 2). A complete vaginectomy was then performed with no further evidence of malignancy being present in the tissue removed.

She has been followed for 15 months in the postoperative clinic. She has remained asymptomatic, there is no lesion demonstrable in the operative site, and Papanicolaou smears have remained negative.

Comment

The criteria for the diagnosis of primary carcinoma of the vagina as set up by the Radiological Subcommittee of the Committee on Hygiene of the League of Nations, as modified in 1932,¹ are: (1) site of growth in the vagina; (2) clinical examination showing the cervix to be intact; (3) no grounds for supposing it to be other than a primary growth in the vagina.



Fig. 2. Vaginal mucosa from biopsy on Nov. 7, 1958. The histologic changes are essentially the same as those in 1956.

The diagnosis of vaginal carcinoma is usually made by biopsy, but Palumbo,² and Cuyler and associates³ showed that cytologic studies on the vaginal secretions on 13 proved cases gave a correct diagnosis in 11 of the cases (92.6 per cent). There was one false-negative diagnosis (8.4 per cent), which compares favorably with the incidence of error in proved cases of carcinoma of the cervix. Palumbo did state that these two malignant growths cannot be differentiated by cell studies, but, if malignant cells of endocervical origin were found, the probability of having a cervical malignancy is greater. Even more impressive is the fact that Palmer and associates¹ diagnosed 2 cases of primary vaginal carcinoma when no tumor was evident clinically. He did cytologic studies on 6 proved cases of carcinoma, and there was only one false-negative smear. He believed this to be a very valuable method of follow-up for residual or recurrent tumor.

The case presented in this report appears to meet all the criteria for the diagnosis of primary intraepithelial carcinoma of the vagina, viz., the biopsy before operation, histologic description of the operative specimen

showing the lesion to be separate from the cervix, and the cervix, tubes, and uterus free of malignancy.

From the available data, it is not possible to determine whether the carcinoma in situ present in 1958 represented a residual lesion which had extended in the 2 years subsequent to hysterectomy or whether it represented new areas of neoplastic changes.

Conclusions

Primary intraepithelial carcinoma of the vagina is a most unusual condition, not only because of the rarity of carcinoma in this location, but because the very nature, characteristics, and location of this tumor make its diagnosis in the early stages difficult. Cytologic studies appear to be as accurate in vaginal carcinoma as in carcinoma in situ of the cervix. The follow-up on all patients treated for cancer of the vagina and cervix should include Papanicolaou smears to detect early recurrence and inadequate treatment.

Because of the rarity of this condition, an outline of therapy cannot be given unequivocally.⁴ Because of the possible recurrence or incomplete excision following par-

tial vaginectomy in the patient presented here, total vaginectomy became necessary. In some younger women, when delay of definitive treatment is sought for one reason or another, partial vaginectomy plus careful follow-up with cytologic studies may be considered.

Summary

1. Primary carcinoma of the vagina is briefly discussed.

2. A case of intraepithelial carcinoma of the vagina is presented. The presence of the

same condition 2 years postoperatively may be due to recurrence or incomplete excision during the initial therapy.

3. A plea is made for careful evaluation of every area of the vaginal mucosa combined with cytologic studies in every gynecologic examination, especially in those women who complain of vaginal discharge and/or painless bleeding.

4. The value of cytologic studies in the diagnosis and posttreatment follow-up is stressed in primary or secondary vaginal carcinoma.

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Relation of carcinoma in situ of the vagina to the early diagnosis of vaginal cancer

Report of a case

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CARCINOMA of the vagina is so rare that it is not listed separately as a cause of death in the Vital Statistics of the United States. It accounts for between 1.0 and 1.6 per cent^{1, 2} of all genital tract malignancies, yet in many clinics it is not seen even this frequently.

While primary vaginal carcinoma is, indeed, unusual, intraepithelial vaginal lesions are even more rare. The authors can find only one³ well-substantiated case in the literature. The case herein reported was submitted to the Armed Forces Institute of Pathology, which now has only 13 such examples catalogued.⁴

Since the uniformly poor prognosis of vaginal cancer is probably a reflection of late diagnosis, more extensive use of exfoliative cytology offers the hope that this condition will be diagnosed more readily and at an earlier stage in the future. Because the present case was actually diagnosed as "intraepithelial epidermoid carcinoma" on the basis of examination of the routine genital smear, it was thought to be worth reporting.

A 71-year-old white woman, para 3-0-3, was seen in the Out-Patient Gynecology Service of the University-Hillman Clinics because of vulvar irritation and a thin watery vaginal discharge of minimal amount. Complaints referable to the present illness were first noted 2 to 3 months prior to her initial clinic visit.

Her past medical history was unremarkable. No bleeding, spotting, or staining had been noted since her menopause 20 years previously. The review of systems was otherwise negative and the family history pertinent only in the death of a sibling from carcinoma of the cervix some years ago.

Physical examination revealed vital signs within the norm and the general physical findings of a patient in this age group.

Pelvic examination disclosed patchy, minimal, vulvar erythema, and the Bartholin's, Skene's, and urethral glands were not remarkable. The vaginal mucosa was nonestrogenic and the atrophic cervix lay flush with the vaginal vault, presenting no visible abnormalities. Bimanual examination disclosed a small uterus and no abnormal findings were noted in the adnexa.

The routine cervical and vaginal cytologic preparations were made, and the presence of large atypical epithelial cells with high nuclear-cytoplasmic ratios prompted the diagnosis of "Class IV, intraepithelial epidermoid carcinoma." These cells (Fig. 1) showed relatively

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heavy aggregates of chromatin in an otherwise vesicular background. Mitotic figures were not encountered in the smear and precise localization of the malignancy could not, of course, be offered, although it was assumed by both the gynecologist and surgical pathologist that the malignancy was cervical.

The patient was, therefore, admitted to the Gynecology Service of the University Hospital and on July 11, 1959, the patient was given general anesthesia for dilatation and curettage. Pelvic examination at this time disclosed several patchy, erythematous areas in the vaginal mucosa. These areas were not raised and did not bleed from the surface traumatization of the preparatory cleansing measures. A uterine sound could be passed only to a depth of 2 cm. Curettage was attempted, but no endometrial tissue was obtained. The cervix was coned by the cold-knife technique and a punch biopsy of the largest of the erythematous lesions was obtained. The two specimens were submitted as "endometrial scrapings" and "cervical biopsy." The surgical pathology diagnosis was "epidermoid carcinoma of the cervix, intraepithelial," and "endometrium inadequate for diagnosis."

The gynecologist consulted the surgical pathologist because he suspected that perhaps an error in labeling had occurred in the operating room or that the biopsy of vaginal mucosa had not been submitted. There are no histologic features by which vaginal mucosa can be distinguished from the pars vaginalis of the cervix, and since therapy for preinvasive carcinoma of the 2 areas is quite different, it was decided to repeat the biopsy. The surgical pathologic diagnosis of a second biopsy of the vaginal lesion was "epidermoid carcinoma, intraepithelial."

The second biopsy showed essentially the same histologic features as the first, but the problem of location had been resolved by accurate labeling of the specimen. Atypical epithelial cells (Fig. 2) showed evidence of growth activity up to the vaginal surface where the cells lay with their long axes directed perpendicularly to the surface. Occasional mitotic figures were seen in these anaplastic cells and the arrangement was essentially the same as that in the commonly encountered intraepithelial carcinomas of the cervix. The fact that these cells did not stain positively by the McManus⁵ technique or the Mowry⁶ procedure precluded their possible origin from metastatic ovarian cancer.

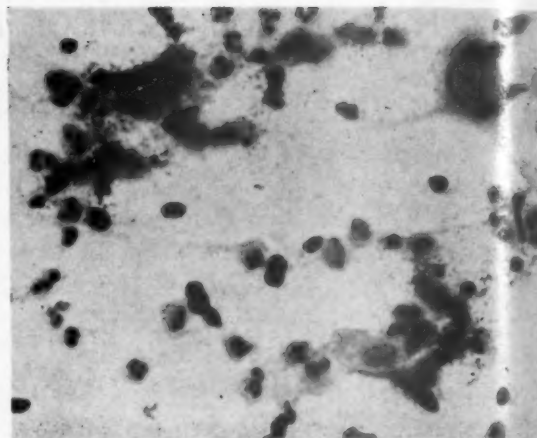


Fig. 1. Photomicrograph of Papanicolaou smear showing presence of large atypical epithelial cells with high nuclear-cytoplasmic ratios.

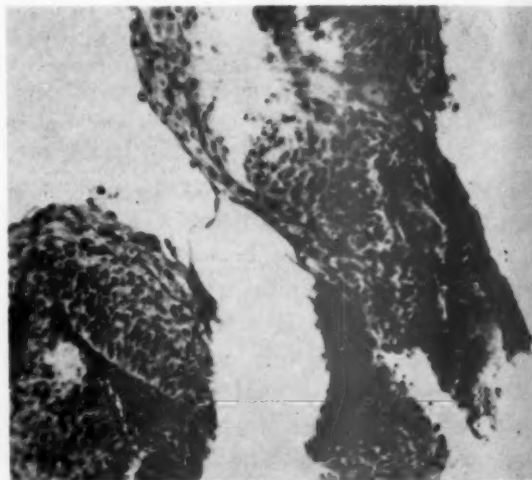


Fig. 2. Photomicrograph showing evidence of occasional mitotic figures and anaplastic cells. These atypical epithelial cells lie with their long axes directed perpendicularly to the surface.

On July 28, 1959, a total vaginectomy, vaginal hysterectomy, and bilateral salpingo-oophorectomy were performed with minimal difficulty, and a Penrose drain was left in the vaginal suture line. The patient recovered without incident and was discharged on the eighth post-operative day.

The final diagnoses were: (1) epidermoid carcinoma, intraepithelial, of vagina; (2) uterus showing: (a) cystic atrophy of endometrium, (b) acute (postbiopsy) and chronic cervicitis; (3) cystadenoma of right ovary; (4) cystic left ovary; (5) Fallopian tubes.

The margins of resection were free of tumor. The specimen was studied by the multiple block,

step section technique to exclude invasion. As seen in Fig. 3, invasion was not demonstrated and the adjacent vaginal mucosa was atrophic.

Comment

Unique among mucosal structures in its low incidence of primary carcinoma, the vagina is subject, probably, to more diverse traumatizing agents and to more actual trauma than other structures such as the oral cavity, esophagus, and cervix, which are histologically so similar. Douches, coitus, and childbirth are the more obvious factors of physical trauma. Infections caused by different specific etiological agents are frequently encountered at all stages of life. Moreover, as shown by Papanicolaou and Traut,⁷ the cytology of vaginal mucosa undergoes cyclic changes associated with puberty, estrus, and menopause. Despite these factors, which could be (and have been) linked with carcinogenesis of other mucosal structures, the vagina remains an infrequent site of primary malignancies. If the well-documented theory^{8, 9} of cervical carcinoma in situ being the forerunner of invasive cervical carcinoma is accepted, together with the studies of Auerbach,¹⁰ relating preinvasive to invasive bronchogenic carcinoma, then the principle must carry to the vagina and recognition of preinvasive cancer would have the obvious beneficial results.

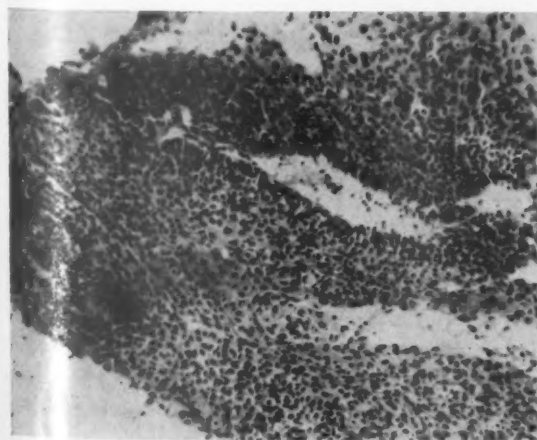


Fig. 3. Photomicrograph again demonstrating the perpendicular arrangement of anaplastic cells. Adjacent to these areas is atrophic vaginal mucosa. Invasion is not present.

This recognition will follow, in a certain number of cases, adequate analysis of two problems: namely, the clinically false-positive cytology report and the histologically false-positive cytology report. It is well known that Class IV diagnoses of intraepithelial epidermoid carcinoma may be made on cervical smears in the face of cervixes which appear perfectly normal to visual examination.^{11, 12} When the cytologic examination has been performed by trained cytologists and confirmed by the surgical pathologist,¹³ the danger of upgrading in genital cytology is minimal and the diagnosis is usually proved by subsequent histologic study of the coned cervix or endometrial curettings.

When, however, adequate cervical biopsy and curettage fail to disclose the source of atypical cells, then prompt evaluation of the remainder of the genital tract is in order. Since so few instances of intraepithelial vaginal cancer are on record, little is known of the clinical appearances of the lesion. In the present case, clinically apparent lesions were observed on the second pelvic examination and it is indeed possible that, under less fortunate circumstances, these might not have been detected and vaginal biopsy not performed.

The treatment accorded this patient is, in essence, the treatment given to patients with intraepithelial lesions of any site and does not differ basically from the standard treatment prescribed for patients with small and early superficial melanomas,¹⁴ intraepithelial lesions of the larynx,¹⁵ or intraepithelial lesions of the cervix.¹⁶ Adequate operation consists of excision of the local area of tumor with an adequate border of uninvolved tissue. In the case of intraepithelial carcinoma of the vagina, certain topographic and technical features make hysterectomy virtually obligatory to meet the criteria of adequate local excision.

Summary

1. A case of preinvasive vaginal carcinoma is presented.
2. The diagnosis was made conclusively

on the basis of cytologic examination of a routine preparation.

3. Final diagnosis resulted from cooperative efforts of gynecologists, cytologist, and surgical pathologist.

4. The rarity of vaginal carcinoma in general and preinvasive vaginal carcinoma in particular is discussed.

5. The importance of adequate evaluation of cytologic evidence of genital malignancy is emphasized.

6. Therapy of intraepithelial vaginal carcinoma differs in no way from therapy of other intraepithelial lesions, and consists of adequate local extirpation of disease.

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Squamous cell carcinoma of the vagina following vaginal hysterectomy for intraepithelial carcinoma of the cervix

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IN THE past decade, carcinoma in situ of the cervix has been the subject of intensive investigation. In spite of this, there is no universal agreement on its clinical course, management, or even pathologic features.

This case is added to the growing list of reports citing the occurrence in the vagina of intraepithelial and invasive carcinoma following hysterectomy for cervical carcinoma in situ. It is unusual because of the rapidity with which the invasive vaginal carcinoma appeared, and it somberly demonstrates that immediate investigation of positive post-therapy cytologic findings is of utmost importance.

Case report

The patient, a 36-year-old white woman, gravida i, para i, was seen in the Out-Patient Clinic at Harper Hospital on Nov. 17, 1958, complaining of menorrhagia for the preceding year. Findings on physical examination were normal except for an erosion of the anterior lip of the cervix. Malignant cells were demonstrated by Papanicolaou smear of the cervix and vagina.

On Dec. 4, 1958, a cold cone biopsy of the cervix was performed with dilatation and curettage. The cone specimen was divided into 12 sections which were immediately frozen and ex-

amined. Several sections revealed carcinoma in situ of the cervix. Vaginal hysterectomy was performed immediately, a vaginal cuff of at least 0.5 cm. being included in the specimen. Permanent sections showed squamous carcinoma in situ of the vaginal mucosa extending to the edge of the specimen (Fig. 1).

Further studies were not undertaken immediately after operation because of a severe anxiety reaction. She was followed as an outpatient at 3 to 4 week intervals. On April 8, 1959, another Papanicolaou smear of the vaginal vault was taken, showing malignant cells (Fig. 2). The patient was not readmitted until July 8, 1959, because she sought the services of a faith healer. Pelvic examination on admission revealed a roughened area 2.5 cm. in diameter on the posterior vaginal wall. This area failed to stain with Lugol's iodine. Partial colpectomy including the nonstaining area was performed on July 9, 1959. The histologic examination demonstrated early invasive squamous carcinoma of the vaginal wall (Fig. 3). On July 17, 1959, external roentgen therapy was begun and the patient received 5,100 r tumor dose over the next 4 months. On pelvic examination Dec. 9, 1959, no evidence of carcinoma was found, and cytologic studies showed good radiation reaction with no evidence of carcinoma.

Comment

Although the pathologist has recognized carcinoma in situ of the cervix for over half a century, its clinical significance still is not

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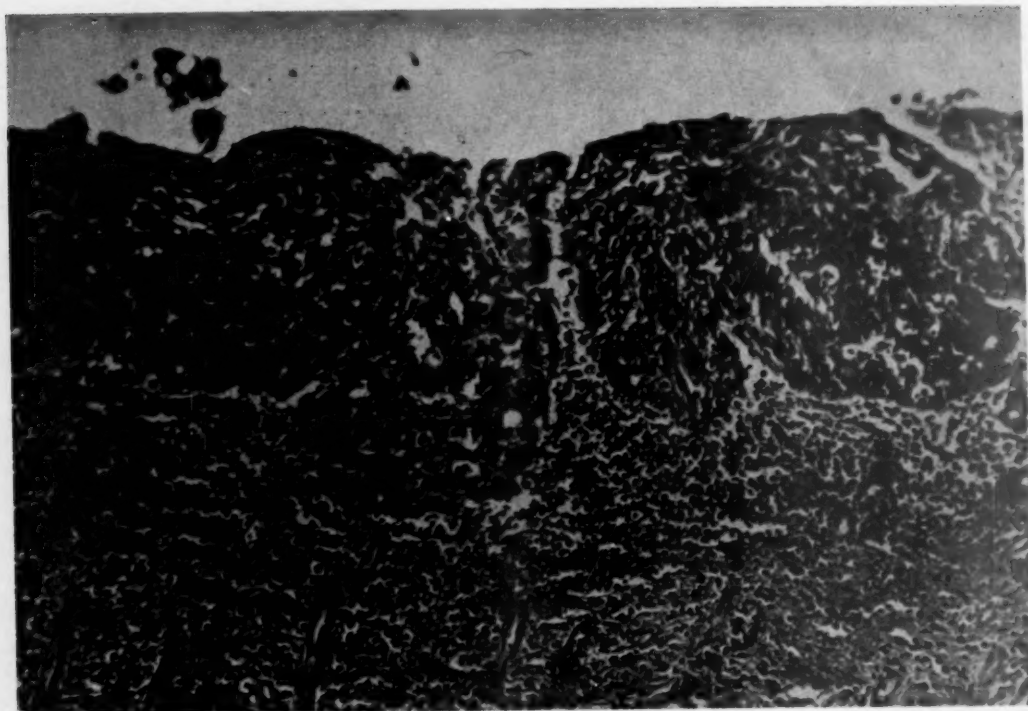


Fig. 1. Cervical carcinoma in situ showing typical neoplastic epithelial changes and an intact basement membrane. Note the inflammation in the superficial cervical stroma. (Original magnification $\times 129$.)

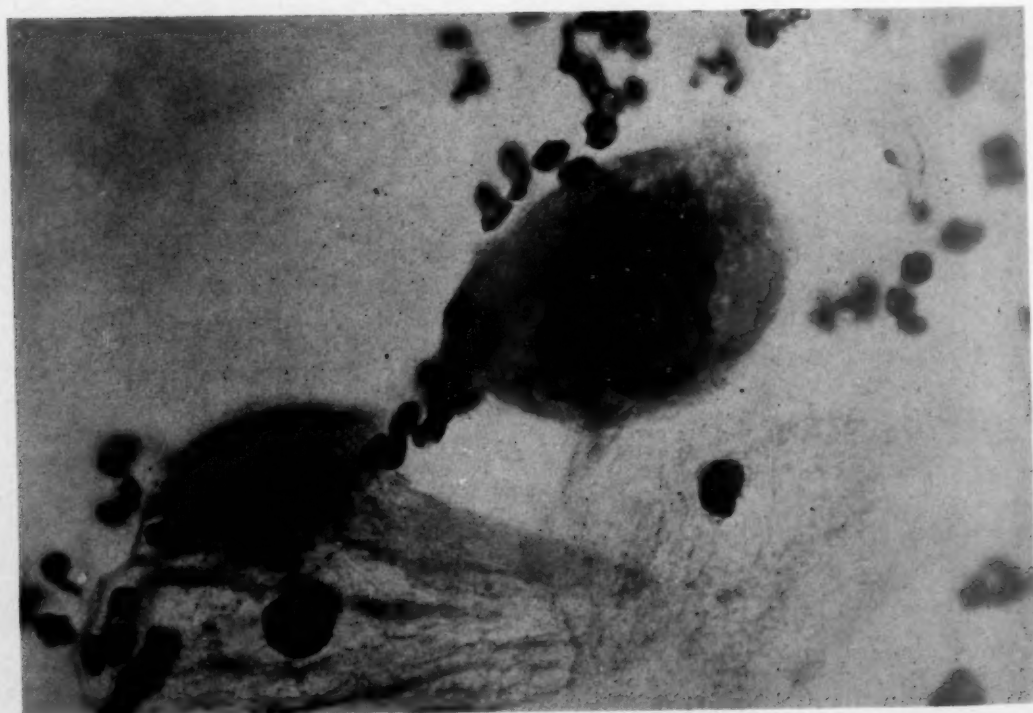


Fig. 2. Malignant cells from vaginal vault. Note one cell showing elongation. (Papanicolaou stain. Original magnification $\times 1,215$.)

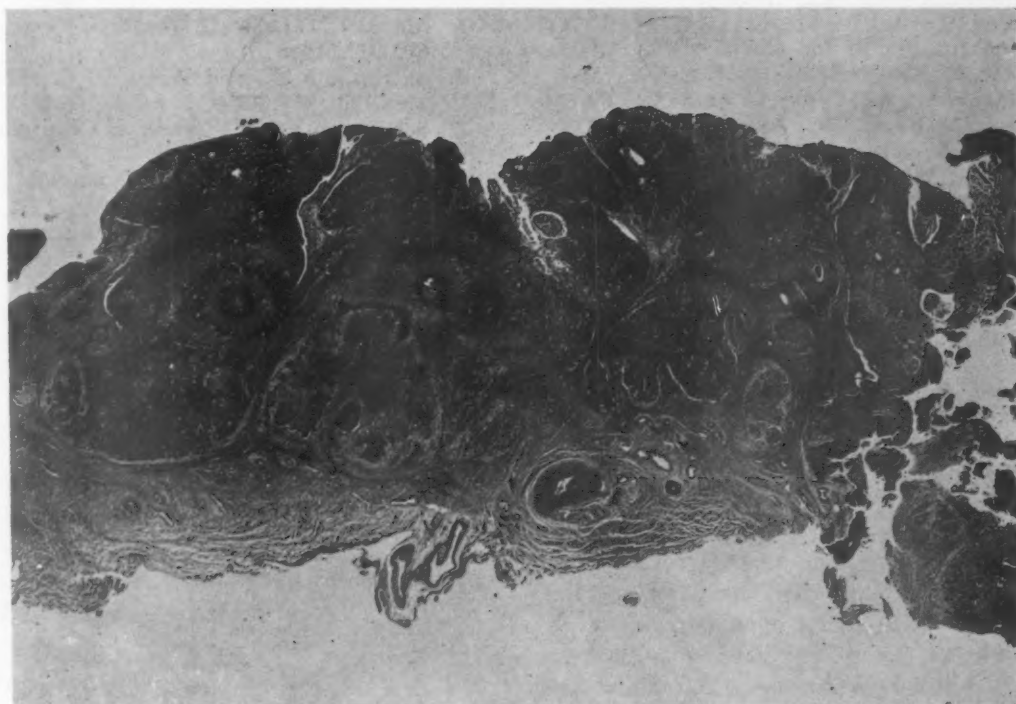


Fig. 3. Photomicrograph showing the invasive nature of vaginal squamous cell carcinoma. (Original magnification $\times 12$.)

clearly understood. Schiller⁸ was convinced that it represented the early stage of invasive carcinoma and reported two recurrences after rather extensive operation as evidence of this belief. Since this time, recurrences following all manner of management, from simple biopsy to full irradiation, have been reported.^{1, 2, 3, 5, 7, 9, 10}

We do not wish to enter the controversies as to whether intraepithelial carcinoma becomes invasive or the invasive disease arises more frequently in its presence, or as to whether conization or extended hysterectomy represents the management of choice. The fact that many patients treated for intraepithelial carcinoma have early invasive disease on more thorough investigation has been substantiated repeatedly.^{4, 7} We do not deny that invasive vaginal disease may have been present at the time of vaginal hysterectomy.

An intensive program of pre- and post-therapy investigation, regardless of the method of management, should markedly diminish such occurrences. The following regimen should provide an adequate prophylactic program:

1. Iodine staining and biopsy of all non-staining areas at the time of cold cone biopsy.⁶
2. Investigation of at least 12 sections of cone material to determine extent and possible invasion.
3. After definitive operation (if further surgical procedures are undertaken), microscopic examination of the entire circumference of the vaginal cuff.
4. Cytologic studies at 1, 3, and 6 months after therapy and at yearly intervals thereafter.
5. With return of positive cytologic findings, immediate iodine staining and excisional biopsy of nonstaining areas.
6. Appropriate definitive therapy as indicated by results of biopsy.

Summary

A case of invasive carcinoma of the vagina 6 months after vaginal hysterectomy for intraepithelial carcinoma of the cervix is reported.

An active program of pre- and post-therapy investigation is presented.

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Five-year cure of a primary malignant melanoma of the vagina by local radioactive isotope therapy

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OCCASIONALLY a dramatic and unexpected cure of a cancer is effected by unorthodox therapeutic methods. Such is the apparent accomplishment in the case reported here.

The patient had an extensive malignant melanoma arising in the vagina. This is an extremely rare form of cancer, only about 30 cases having been reported to date. As far as can be determined from a perusal of the literature, there have been no 5 year cures reported for this type of neoplasm. I recently reported on a patient living and well after radical hysterectomy and vaginectomy for primary vaginal melanoma.¹ Mino, Mino, and Livingstone^{3, 4} reported on one who developed a recurrence 5 years and 3 months after a pelvic exenteration for a melanoma. Simmons⁵ reported a case of malignant melanoma of the vulva which had spread to the vagina and cervix and was treated by radical extirpation; this patient is living and free of cancer 9 years post-operatively.⁶

The case described here is of interest because treatment was instituted solely for palliative effect. The response to the treatment was startling; the melanoma disappeared completely.

Case report

History. The patient was a 47-year-old woman on whom a hysterectomy had been performed 5 years previously for uterine fibroids. Two years previously a left radical mastectomy was performed for carcinoma of the breast. There had been no recurrence of or metastases from the breast cancer.

The present illness dated back 4 months, at which time she developed spotting per vaginam. The vaginal discharge increased in quantity and was sanguineous and extremely irritating to the patient. She consulted a gynecologist, who found the entire vault of the vagina to be filled with a huge, ulcerated, fungating, friable, foul mass. It extended through the right fornix, pressing against or possibly infiltrating the bladder in this region. It measured approximately 6 cm. in diameter and had a shaggy, necrotic surface. The entire posterior vaginal wall was discolored a solid black.

A biopsy specimen was taken which revealed the lesion to be a malignant melanoma (Figs. 1 and 2).

A surgeon was called in consultation who advised that the only procedure that could be attempted with a view to cure was total pelvic exenteration. This was refused.

The patient was referred to me for palliative treatment, her family having been informed of the hopelessness of the situation.

Treatment. Treatment was instituted with the sole expectation of decreasing or stopping the foul, irritating vaginal discharge of which the patient complained bitterly. She had no other complaints; her energy, strength, appetite, and bladder and bowel habits were all normal.

Although I realize that melanomas are radio-resistant, nevertheless, treatment was instituted with radioactive isotopes. On May 3, 1956, 8 mc. of radioactive chromic phosphate plus 10 mg. of thioTEPA was injected into the large, black mass. The patient stated that following this injection she felt a sensation of pelvic distention that lasted about 2 days but that the vaginal discharge ceased completely. A scintigram performed over the abdomen and pelvis on May 14 revealed that all of the activity persisted in the region of the right fornix. Counts

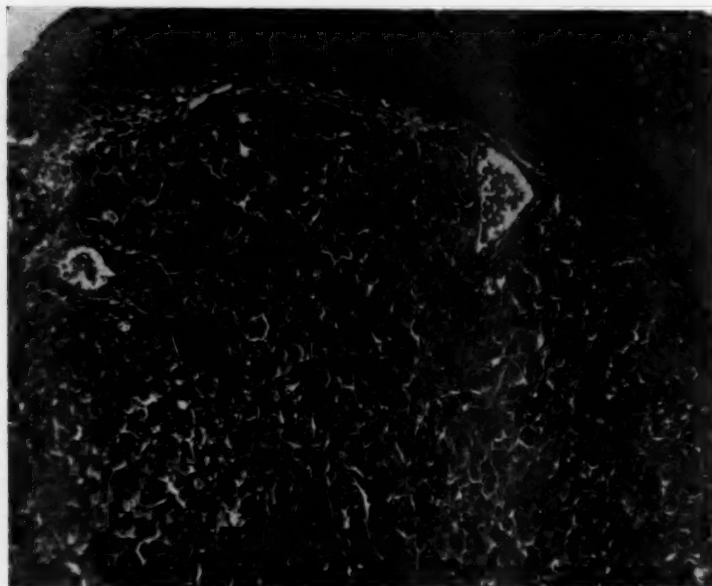


Fig. 1. Low-power photomicrograph of the primary vaginal melanoma. ($\times 175$; reduced $\frac{1}{4}$.)



Fig. 2. High-power photomicrograph of biopsy of primary lesion. Note melanin pigment throughout section. ($\times 400$; reduced $\frac{1}{4}$.)

in the vicinity of this region were equivalent to those of the background. This finding demonstrated that radioactive phosphorus administered as chromic phosphate remained localized at the site of injection.

On June 1, 1956, 10 gold radon seeds, each measuring 1 mc., were injected into the melanoma. The mass began to shrink and interstitial

treatment with radioactive isotopes was continued. On Jan. 18, 1957, 6 mc. of chromic phosphate in a volume of 3 c.c. was injected into the residual tumor mass. The melanoma continued to shrink until March 1, 1957, at which time a firm 1.5 cm. nodule persisted in the left upper portion of the vagina. Five millicuries of radioactive chromic phosphate in a volume of

4 c.c. was injected into this residual mass, which resulted in its complete disappearance. The treatment was given over a period of 10 months.

With the complete disappearance of the mass, treatment was next directed at controlling the melanoma infiltration of the posterior vaginal wall, which was solidly black. It was feared to give external irradiation because of the possibility of producing a rectovaginal fistula. Accordingly, it was decided to treat this region by the use of irradiation derived from radioactive phosphorus (P^{32}) which emits a pure beta ray that has a maximum penetration of 8 mm. Eight millicuries of P^{32} was saturated into ordinary white blotting paper, which blotter was then inserted into the vagina so that it came in contact with all of the posterior vaginal wall. The remainder of the vaginal cavity was packed with ordinary gauze. The blotter was placed in position on April 4, 1957, and removed on April 8, a total of 96 hours, and it is estimated that the surface of the vaginal wall received 40,000 rads. A brisk erythematous reaction developed in the vagina and on April 19, evidence of disappearance of the blackened areas was apparent. The discoloration gradually decreased until July 15, 1957, at which time a tiny blackish spot measuring 2 mm. in diameter remained; this spot eventually disappeared.

The patient was last seen on May 6, 1961. She was then entirely free of any evidence of cancer and the vaginal tissues appeared normal in every respect, except for pallor of the mucosa due to the irradiation.

Comment

This represents a dramatic disappearance of an extensive malignant melanoma primary in the vagina after treatment by interstitially

administered radioactive isotopes in the form of colloidal radioactive phosphorus ($Cr-P^{32}O_4$) and irradiation with P^{32} blotting paper. The patient remains well and free of any evidence of cancer 5 years after the beginning of treatment and 4 years and 1 month after the completion of therapy. Although 10 mg. of thioTEPA was given at the first treatment, this dose is so small that it is doubtful if it contributed to the final outcome.

Summary

The extreme rarity with which malignant melanoma primary in the vagina is being cured and the success attained by interstitial radioactive isotope therapy in this instance would appear to warrant more frequent utilization of this method of treatment in this form of cancer. Although this may have been a "freak" reaction such as occasionally occurs in oncology, the results are nevertheless so startling that no patient whose cancer is inoperable should be denied an attempt at such therapy.

Freund, Kegel, and Dugger² in 1959 attempted cobalt irradiation of malignant vaginal melanoma and claimed good palliation from it but both of their patients developed extensive metastases and died within 7 months of the termination of treatment. The best results can be expected by radical surgical extirpation; but it is suggested that any patient who is not a candidate for surgical extirpation should receive interstitial isotope therapy combined, possibly, with external irradiation.

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Relationship of adenomyosis uteri to endometrial hyperplasia and endometrial carcinoma

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EVER since its clinical significance was stressed many years ago by Cullen,⁵ adenomyosis uteri has been an entity familiar to gynecologists. However, certain aspects of this lesion still await clarification. In particular, its association with, or relationship to, other fairly common uterine growth processes has received little investigative attention. Considering that adenomyosis is an entity involving activity of endometrial glands (in addition to endometrial stroma) it should be of import to learn the relativity of adenomyosis and other uterine pathology involving endometrial glands, namely, endometrial hyperplasia and endometrial carcinoma.

The purpose of this study was to determine (1) the incidence of adenomyosis in uteri containing endometrial carcinoma compared with its incidence in nonmalignant uteri; (2) whether a relationship exists between the extent of the adenomyosis and the invasiveness of the endometrial carcinoma in uteri containing both processes; (3) the incidence of simultaneous occurrence of adenomyosis uteri and endometrial hyperplasia in uteri with endometrial carcinoma and in uteri without malignancy; (4) the incidence of simultaneous hyperplasia of the endometrium and hyperplasia of the adenomyotic glands; and (5) the possibility of transitions toward or development of anaplasia in adenomyotic glands.

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Introduction

The histogenesis of adenomyosis uteri has heretofore been the theme of much controversy, although it is now generally accepted that adenomyosis originates directly from the lining endometrium and grows into the myometrium, with a concomitant growth response of the latter. Certain early investigators had considered the origin of the ectopic endometrium to be Wolffian duct rests, while others incriminated Müllerian duct remnants. Critical examination of serial sections, however, frequently reveals direct continuity between the glands of the endometrium and the ectopic glands within the myometrium.

The stimulus for this benign glandular invasion is unrecognized. One may speculate that adenomyosis is the result of an excess of a normally present growth factor or an exaggerated response to it, or that it may be the consequence of a diminution in the host resistance to benign glandular invasion. Since estrogen is responsible for endometrial and myometrial growth, it is not unreasonable or unexpected that this hormone has been implicated in the pathogenesis of adenomyosis. Some support is given to this surmise of hormonal influence by the cyclic response to estrogen which adenomyotic glands occasionally demonstrate and by the symptomatic improvement which may occur with the menopause. It is conceivable that alterations in ovarian physiology may prevail in adenomyosis.

There is notable variation in the reported incidence of adenomyosis. Recent surveys

have noted incidences of 10,¹⁵ 21,² and 28¹⁴ per cent in routine surgical specimens. A 53.5 per cent incidence in necropsy material had been reported earlier.¹⁹ Variance in histologic criteria doubtless accounts for some of the discrepancies in reported incidence. Some pathologists require that, to constitute true adenomyosis, the ectopic glands and stroma must be at least one, or even two, low-power fields from the endometrium. However, with small or atrophic uteri, such a stringent criterion might exclude genuine cases of adenomyosis merely because of the thin uterine wall, i.e., ectopic glands and stroma might be situated well within the myometrium but less than one or two low-power fields from the endometrium. An additional criterion used by certain pathologists is that a significant degree of muscle hypertrophy be present about the glands and stroma.

In the course of examination of uteri removed for carcinoma of the endometrium, it became manifest that adenomyosis was observed in these uteri more often than would have been anticipated. However, if one gives credence to a part played by estrogen in adenomyosis and considers at the same time the reports and studies concerning the role of this hormone in endometrial carcinoma,^{9, 12} the simultaneous occurrence of these two lesions need not be surprising. Nevertheless, there is a paucity of critical inquiries regarding the relationship between endometrial carcinoma and adenomyosis uteri. Recently, Giammalvo and Kaplan¹⁰ published one of the few reports relating to this subject. They found a 33 per cent incidence of adenomyosis in a group of cases of endometrial carcinoma compared with an 18 per cent incidence in the control group. This difference is statistically significant.

If one implicates estrogen in the pathogenesis of adenomyosis, it is then natural to explore the possible coexistence of adenomyosis with endometrial hyperplasia, a lesion in which estrogen has been strongly implicated. Although there is considerable morphologic difference between adenomyo-

sis and endometrial hyperplasia, both lesions fundamentally involve abnormal activity of endometrial glands and stroma. The age incidence of adenomyosis parallels that of endometrial hyperplasia. Emge⁸ noted that endometrial hyperplasia is most common at an age when the incidence of myomata uteri is declining. In his report on his study of adenomyosis, he observed hyperplasia of the endometrium in 24 per cent of adenomyotic uteri. Novak and de Lima²¹ reported a 25 per cent incidence. The range of reported incidences for simultaneous endometrial hyperplasia and adenomyosis is 0.8²³ to 54¹⁶ per cent. Novak and de Lima also made the pertinent observation that there was simultaneous hyperplasia of the endometrium and of the heterotopic glands in 36 per cent of the adenomyotic uteri, suggesting the possibility of a common etiological factor.

Examination of endometrial hyperplasia reveals that the contour of the basalis is much more irregular with greater down-growth and "poking inward" by the glands than is seen in the proliferative phase of the menstrual cycle. There is no submucosa in the uterus and the endometrial glands lie in direct contact with the myometrium. Yet there must prevail, even in endometrial hyperplasia, a restraint to actual penetration of the glands into the myometrium. The reason for the seeming ineffectiveness of this barrier in adenomyosis is enigmatic.

Material and method

The material for study included 100 consecutive cases of adenocarcinoma of the endometrium treated surgically at the New York Lying-In Hospital during the years 1954 to 1959. Cases were acceptable provided: (1) there was sufficient benign endometrium for appraisal; (2) there was no history of prior irradiation of any kind; (3) the patient had not received any hormonal therapy; and (4) both ovaries were available for study and were not involved by any hormone-producing neoplasm. The control group was composed of 100 consecu-

Table I. Age distribution of patients

Age (years)	Carcinoma group	Control group
30-39	4	3
40-49	20	24
50-59	41	45
60-69	28	25
70-79	7	3
Total	100	100

tive patients operated upon for a variety of benign pelvic diseases during the same time period. Identical criteria of acceptability were utilized for the control group. The age distribution of the patients in the two groups is indicated in Table I.

Muscular hypertrophy or hyperplasia about the islands of glands and stroma was not considered a prerequisite for the diagnosis of adenomyosis. Such a lesion which Novak²² considers to be an adenomyoma was, however, included in this series when encountered. Cases were excluded if there was any suspicion that the glands and stroma appeared to be located in an ectopic manner because of the direction of the tissue section, even though sections were routinely taken perpendicular to the endometrial lining.

Adenomyosis, histopathologically, is considered "slight" if the process is seen to extend inward to a depth of one third of the thickness of the uterine wall, "moderate" if two thirds inward, and "extensive" if the glands and stroma reach the outer third of the uterine wall. The same terminology and criteria are employed to categorize uterine invasion by endometrial carcinoma. In certain cases in this study, however, it was difficult to designate the adenomyosis with satisfactory precision as being "moderate" or "extensive." For this reason, two categories were employed: "slight" adenomyosis and "moderate to extensive" adenomyosis, referring to penetration of the inner one third and outer two thirds of the myometrium, respectively. It should be noted, however, that in a certain number of cases there was no question that the lesion fell into the

"extensive" category, i.e., penetration of the outer one third, and these cases were so designated secondarily in order to be subjected to an analysis which will be treated later in this paper.

Endometrial hyperplasia was diagnosed when the endometrium demonstrated the typical increased number and activity of glandular and stromal elements characteristic of both the adenomatous and cystic ("Swiss-cheese") varieties. In the adenomatous type, budlike outpouching of the glands into the surrounding stroma is noted, with piling up and frequent protrusion of pseudostratified cells into the gland lumen. The cystic variety exhibits a disparity in the size of the glands with small cystic glands interspersed among large dilated ones; the cell lining is usually cuboidal, but occasionally cylindrical, with less cellular overgrowth than is encountered in the adenomatous type of hyperplasia. In both types, frequent mitoses are seen, perhaps more

Table II. Incidence of adenomyosis uteri

Adenomyosis	Endometrial carcinoma (100 cases)	Control group (100 cases)
Present	60	39
Not present	40	61

Table III. Degree of adenomyosis uteri

Adenomyosis	Endometrial carcinoma (100 cases)	Control group (100 cases)
"Slight"	20	25
"Moderate to extensive"	40	14

Table IV. Invasiveness of endometrial carcinoma in the presence of extensive adenomyosis uteri

Degree of invasion by carcinoma	Endometrial carcinoma cases with "extensive" adenomyosis
None	12
Slight	6
Moderate	10
Extensive	6

in the adenomatous variety. The "retrogressive" or "inactive" type of hyperplasia was not included. This sort reveals numerous cystic glands with but a single layer of low, usually flattened epithelium and little, if any, active-appearing stroma; mitoses here are rare.

Results

Relationship of adenomyosis uteri to endometrial carcinoma. Table II records the incidence of adenomyosis uteri in the endometrial carcinoma group and in the control group. Table III indicates the degree of adenomyosis in the endometrial carcinoma group and in the control group.

It is apparent that adenomyosis is discovered more frequently in uteri with endometrial carcinoma than in those without. This difference in incidence is statistically significant at the 1 per cent level by the chi-square formula with Yates's correction (χ^2 equals 8.00). Not only is the adenomyosis greater in incidence in the carcinoma group, but it is more likely to be of greater degree in the carcinoma case than in the benign case. This difference in incidence of "moderate to extensive" adenomyosis between the carcinoma group and the control group (Table III) is statistically significant at the 2 per cent level (χ^2 equals 7.81).

In 34 of the 40 cases of endometrial carcinoma in the group showing "moderate to extensive" adenomyosis, there was unequivocal histologic evidence that the adenomyosis was "extensive" (i.e., the process extended well into the outer third of the myometrium). These 34 cases of "extensive" adenomyosis were analyzed with regard to the degree of invasion by the endometrial carcinoma. The results are presented in Table IV.

These findings denote that there is no correlation between the presence of "extensive" adenomyosis and the degree of invasion by the endometrial carcinoma. These results are noteworthy since it has been speculated by some that adenomyosis allows a facile route for extension of endometrial carcinoma and predisposes the patient to

Table V. Coexistence of adenomyosis uteri and endometrial hyperplasia

Group	No. cases	Adenomyosis and endometrial hyperplasia
Endometrial carcinoma	100	39
Control	100	7

earlier and greater involvement by the carcinoma.

Coexistence of adenomyosis, endometrial hyperplasia and endometrial carcinoma. Table V indicates that adenomyosis uteri and endometrial hyperplasia were coexistent in 39 per cent of endometrial carcinomas. Study of the control group revealed the two lesions concomitantly in 7 per cent of this group. This difference is statistically significant at the 1 per cent level (χ^2 equals 27.13). With regard to this particular relationship, a 12 per cent incidence was cited by Dreyfuss.⁷

The cases in both the carcinoma and control groups which showed concomitant adenomyosis and endometrial hyperplasia were additionally studied to ascertain how often hyperplasia was found in the adenomyotic glands simultaneously with hyperplasia in the endometrium. In the group with endometrial carcinoma, this association was noted in 15 of the 39 patients, while in the control group it occurred in 3 of the 7 patients. The "adenomyotic glandular hyperplasia" was of both the cystic and adenomatous varieties.

Fig. 1 shows a tissue section from a case of endometrial carcinoma in which the benign endometrium, uninvolved by carcinoma, exhibited a typical "Swiss-cheese" form of cystic hyperplasia. Fig. 2 reveals extensive adenomyosis in the myometrium of the same patient, with the ectopic glands demonstrating a hyperplasia identical with that seen in the endometrium in the preceding figure. Fig. 3 demonstrates the cystic hyperplasia of the endometrium appearing to burrow into the myometrium and being continuous with adenomyotic areas also displaying cystic hyperplasia. This case illus-



Fig. 1. Case 1. Endometrial surface showing cystic hyperplasia of the glands. (Original magnification $\times 20$.)

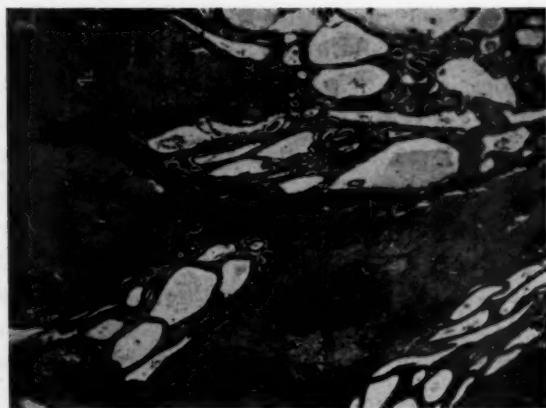


Fig. 2. Case 1. Section of myometrium demonstrating extensive adenomyosis uteri. The glands reveal cystic hyperplasia similar to that in Fig. 1. (Original magnification $\times 20$.)

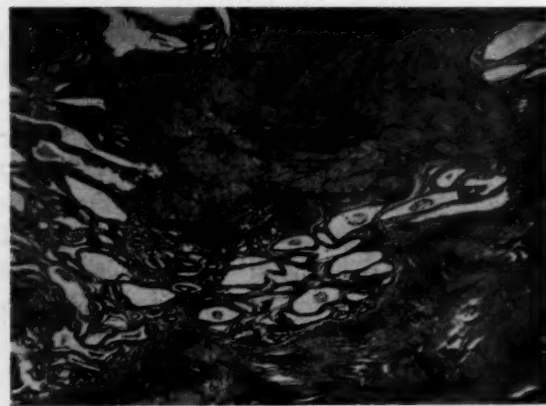


Fig. 3. Case 1. Section through endometrium and myometrium. Note continuity between surface glands (left) and adenomyotic glands. (Original magnification $\times 20$.)

trates, as did others in this series, that a similar growth response may be manifested by identical hyperplastic changes in both endometrial and adenomyotic glands.

The development of anaplasia in adenomyosis. Although the development of carcinoma in areas of external endometriosis has been well documented,^{1, 4, 6, 7, 11, 18, 25} reports of malignant transformation in the glandular epithelium of adenomyotic areas is rare. A recent paper¹⁷ reviewed earlier cases of carcinoma arising within adenomyosis uteri and reported a case which the authors considered to be only the tenth authentic one. Colman and Rosenthal³ recently reported a case of carcinoma in situ in adenomyosis in which this alteration was noted in a single adenomyotic focus, with the endometrium demonstrating benign proliferative glands. It is surprising that there are so few reports of anaplasia developing in hyperplastic glands within adenomyotic foci, considering the plethora of articles suggesting a relationship between endometrial hyperplasia and endometrial carcinoma. The data in this study imply an interrelationship between adenomyosis, endometrial hyperplasia, and endometrial carcinoma. It is logical to conjecture that whatever is significant in the genesis of carcinoma in endometrial hyperplasia might also influence hyperplastic glandular epithelium in adenomyotic areas.

Sampson²⁴ utilized certain criteria for the diagnosis of carcinoma developing in external endometriosis which could be adapted and similarly applied to adenomyosis: (1) evidence of pre-existing endometriosis interna at the site of the supposed malignant lesion; (2) exclusion of the possibility of the carcinoma representing an invasion or metastasis from another location; (3) evidence of transitions between the benign and malignant glandular structures; and (4) both glands and stroma must be present to constitute genuine adenomyosis. While Sampson's original criteria are ostensibly valid, his criterion pertaining to the non-existence of any carcinoma elsewhere may not be applicable at the present time, since

it precludes the possible simultaneous occurrence of carcinoma in situ both in the endometrium and in areas of adenomyosis. Since endometrial carcinoma often exhibits multicentricity of origin in scattered foci of endometrial hyperplasia, it is not unreasonable to anticipate that carcinoma might likewise arise simultaneously in normally situated endometrium and in areas of adenomyosis.

Fig. 4 represents the uterine curettings from a postmenopausal patient. An early, well-differentiated endometrial carcinoma was evident, in addition to distinct endometrial hyperplasia and also normal proliferative endometrium. Figs. 5 and 6 are higher power views of the curettings. The anaplastic glands are crowded and reveal large cells whose cytoplasm is pale staining and eosinophilic. No secretory effect is present. The nuclei are fairly large and contain irregularly distributed chromatin; nucleoli are prominent. Anisocytosis is, however, only moderate and there is no marked hyperchromasia. This lesion corresponds to the carcinoma in situ of the endometrium as described by Hertig and co-workers.¹³ Both higher power views, but particularly Fig. 6, reveal transitions between proliferative glands, hyperplastic glands, and glands of carcinoma in situ. Fig. 7 is a section, in the same case, through the uterine wall, revealing many islands of crowded glands with a pale-staining cytoplasm. The glands have a back-to-back arrangement. Fig. 8 is a higher power view of a portion of the preceding figure and shows varying degrees of proliferation and growth of the glandular epithelium. Examination under even higher magnification (not illustrated) showed considerable nuclear activity with cellular disorientation and disparity in size. The over-all pattern bears strong resemblance to that seen in the endometrium although perhaps less marked. The glandular growth and crowding coupled with the cellular activity suggest markedly atypical hyperplasia or early anaplasia. There is a well-defined border of typical endometrial stroma to be noted about each island of

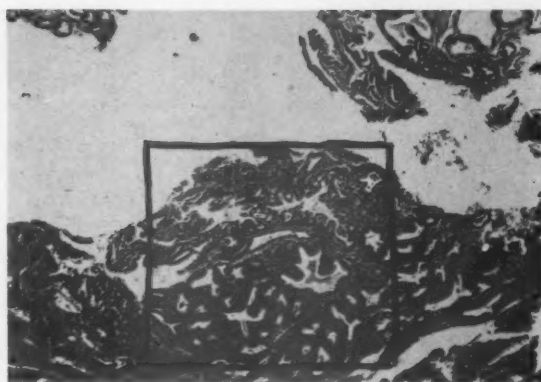


Fig. 4. Case 2. Endometrial curettings in patient 7 years postmenopausal. Note varied glandular pattern. The glands in the enclosed area are paler staining, with crowded, back-to-back arrangement. (Original magnification $\times 15$.)

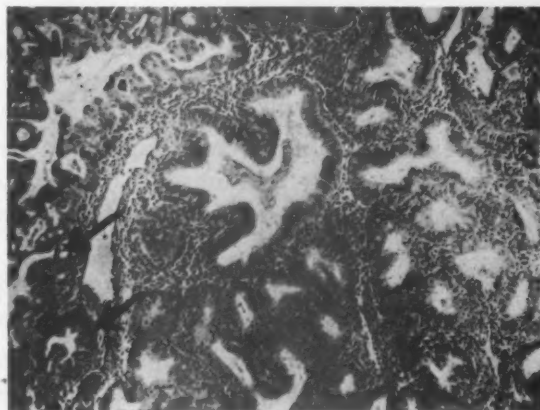


Fig. 5. Case 2. High-power view of enclosed area in Fig. 4. Many glands exhibit anaplasia, particularly those marked by arrows. Note variations in the epithelium within individual glands. (Original magnification $\times 110$.)

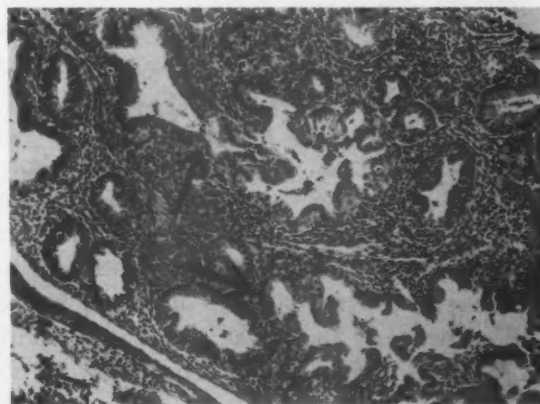


Fig. 6. Case 2. High-power view of another portion of curettings. Note distinct transitions of epithelium, within individual glands, from hyperplasia to anaplasia (arrows) (Original magnification $\times 110$.)

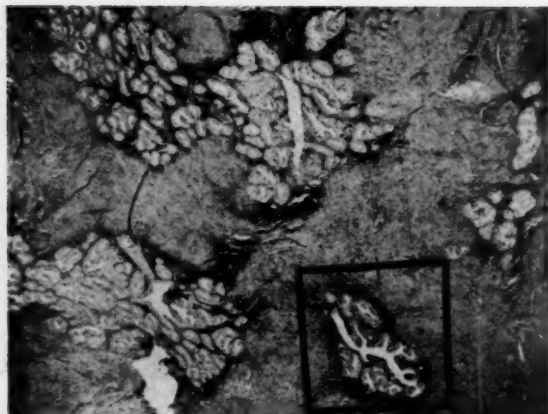


Fig. 7. Case 2. Section through myometrium revealing numerous islands of glands, all of which are encircled by endometrial stroma. Glands are extremely crowded, with back-to-back arrangement. (Original magnification $\times 15$.)

glands in Fig. 7. These atypical glandular areas within the myometrium, therefore, probably arose in adenomyotic foci simultaneously with similar changes in the endometrium.

It is unfortunate that the entire endometrial-myometrial junction in this case was not examined at the time. However, in four sections taken through the uterine wall, there was no instance of invasion of the myometrium by the endometrial carcinoma. In addition, there was no instance of glands deep within the myometrium which were not surrounded by normal endometrial stroma, suggesting that these were truly adenomyotic areas. In invasive endometrial carcinoma, one does not see any such orderly and plenary participation on the part of the stroma as can be seen in Fig. 7; this point is emphasized by pathologists.²⁰ Moreover, the endometrial lesion itself appeared to be of the *in situ* variety of carcinoma. This case is considered perhaps to represent the simultaneous development of anaplasia in the endometrium and in adenomyosis. The following observations seem to sustain this contention: (1) various stages of transition were seen in the endometrium, consisting of proliferative glands, hyperplastic glands, and glands showing carcinoma *in situ*; (2) there were

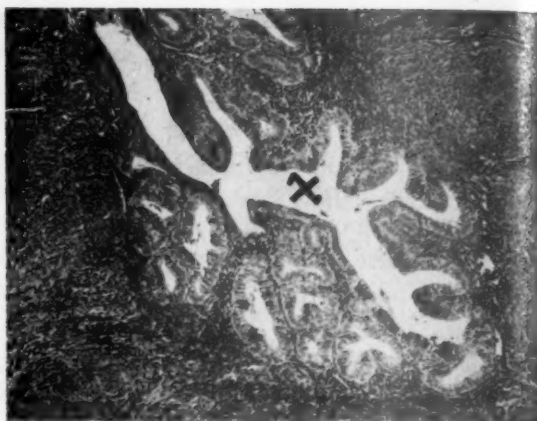


Fig. 8. Case 2. High-power view of enclosed area in Fig. 7. Note pale-staining, atypical glands, some of which exhibit epithelial in-pouching, with cellular disorientation. The large central gland (marked x) reveals distinguishable transitions in its lining epithelium. (Original magnification $\times 100$.)

areas of distinct adenomyosis present as evidenced by endometrial glands and stroma well within the myometrium; (3) stages of transition were noted in the areas of adenomyosis which were similar to those noted in the endometrium; and (4) in the sections available no penetration of the myometrium by malignant glands was observed.

Comment

It thus emerges that adenomyosis uteri is encountered more frequently in uteri with endometrial carcinoma than in those without. Moreover, adenomyosis is usually more extensive in the presence of endometrial carcinoma than in uteri without malignancy. These statistically significant findings might suggest that a common factor or stimulus is involved in the pathogenesis of endometrial carcinoma and adenomyosis. With regard to the possibility just outlined, the data in this study show no correlation between extensive adenomyosis and the extent of invasion by the endometrial carcinoma. Thus, if any background relationship exists between the two lesions, it is not a directly proportionate one.

It would be imprudent, from the evidence here, to entertain the assumption that there is a cause and effect interrelation between adenomyosis and endometrial carcinoma.

Nor can one reconcile the possibility that the uterus destined to develop adenomyosis may also inherit some propensity toward developing endometrial carcinoma. However, one cannot ignore the evidence found here of the frequent coexistence of adenomyosis, endometrial hyperplasia, and endometrial carcinoma. These findings are of notable import in view of the surfeit of publications postulating a hormonal factor for each of the three individual entities.

Adenomyosis is found essentially in the middle-aged woman while endometrial carcinoma occurs predominantly in the older age group. When the associations of these concomitant lesions demonstrated in this study are considered, it is conceivable that prolonged or possibly unopposed action by the stimulus which causes adenomyosis may eventually result in a carcinomatous change within the same uterus. It is also possible that the mere presence of adenomyosis, especially when extensive, may in some unknown fashion render the uterus more susceptible to factors capable of provoking malignant growth. Some support is given to the possibility of a common inception operating in both adenomyosis and endometrial carcinoma by the findings in this study that, in a large percentage of cases in both the carcinoma and the control groups, the adenomyotic glands showed a hyperplasia simultaneously with hyperplasia in the endometrium. Ostensibly, it appears that the potential for aberrant growth is almost as great, or perhaps as great, in adenomyotic glands as in those in their normal mucosal location.

Adenomyosis uteri has often been relegated to a somewhat inconspicuous station in gynecologic pathology. The conclusions which may be drawn from the results of this study suggest that one should approach this lesion with a higher regard for its clinical significance than has heretofore been accorded it.

Summary

1. Adenomyosis uteri is encountered more often in the uterus with carcinomatous endometrium than in one with benign endometrium. In a group of 100 cases of endometrial carcinoma, adenomyosis was found in 60. In a control group of 100 cases with benign endometrium, adenomyosis occurred in 39. This difference is statistically significant.

2. Adenomyosis is more likely to be of greater degree in the presence of endometrial carcinoma than in the uterus with benign endometrium. "Moderate to extensive" adenomyosis was noted in 40 of the 100 carcinoma cases and in 14 of the 100 controls. This difference is statistically significant.

3. No correlation was found between the presence of "extensive" adenomyosis and the invasiveness of the endometrial carcinoma.

4. Adenomyosis uteri and endometrial hyperplasia coexist more frequently in the presence of endometrial carcinoma than in the uterus with benign endometrium. In the group of endometrial carcinomas, 39 cases exhibited both adenomyosis and endometrial hyperplasia compared with 7 cases in the control group. This difference is statistically significant.

5. The possibility of the development of anaplasia in adenomyosis uteri has been considered.

6. These interrelationships between adenomyosis uteri, endometrial hyperplasia, and endometrial carcinoma suggest that a common denominator, possibly hormonal, may exist in the three lesions.

I wish to express my appreciation to Dr. R. Gordon Douglas, Obstetrician and Gynecologist-in-Chief, the New York Hospital, and Professor of Obstetrics and Gynecology, Cornell University Medical College, and to Dr. Stewart L. Marcus for their reviews of this paper.

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Carcinoma of the endometrium

A case study illustrating the evolution of the disease in a 24-year-old woman

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IT IS the purpose of this paper to present a case of carcinoma of the endometrium in a 24-year-old woman, illustrating the progression of the disease which has been followed through the stages of development from its beginning as a mild hyperplasia to the ultimate malignant change, and to suggest a possible etiology. For the first time, it is possible to present a case in which there are not only endometrial biopsies spanning a 10 year period but also ovarian biopsies. Since the case first came under the care of the senior author, the diagnostic studies and the therapy were planned so that sequential tissue studies would be obtained in the event of failure of the intended treatment.

Classically, endometrial cancer is thought to be associated with women in the fifth and sixth decade with only 2 to 5 per cent of the cases occurring under the age of 40.¹⁻³ The youngest patient with true adenocarcinoma of the endometrium reported in the literature was a 16-year-old girl⁴; and, indeed, cases in patients under the age of 30 are extremely rare. By studying a group of cases occurring in younger women, as well as reviewing previous biopsies, a pathogenesis of this disease has been suggested.⁵⁻⁷ In addition to the above changes, one finds that the abnormal menstrual pattern as well as peculiarities of physical habitus are associated in the literature dealing with not

only carcinoma of the endometrium^{2, 3} but also the Stein-Leventhal syndrome.^{8, 9}

In the case under consideration, the patient had an unremarkable childhood with a normal menarche occurring at the age of 12. One year after this the patient received external x-ray therapy to the left breast for "an injury." All that is known of this treatment is that this young girl received daily treatments over a period of weeks. It has not been possible to ascertain the type or the amount of radiation given, but it was sufficient to cause complete atrophy of the left breast. After this the bleeding pattern became progressively irregular to the point that the patient was having alternating episodes of amenorrhea and hemorrhage. By the age of 15, an episode of profuse vaginal bleeding occurred, eventually requiring curettage to control the hemorrhage. The endometrium was interpreted as showing a simple hyperplastic pattern (Fig. 1). Following this the patient's menses remained irregular, but there were no bouts of profuse hemorrhage. After approximately 2 years, she was hospitalized for abdominal pain and underwent laparotomy, at which a normal appendix and hydatid cyst of Morgagni were removed. Later that year, following several months of amenorrhea (age 17), she suffered another bout of vaginal bleeding severe enough to require transfusions and curettage. Findings on physical examination at this admission were described as unremarkable except for a moderately obese habitus. The pathological diagnosis



Fig. 1.

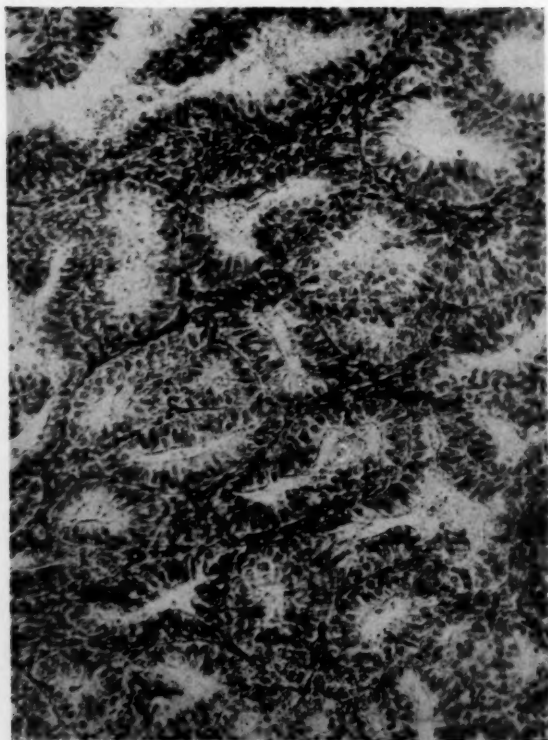


Fig. 2.

made at this time was hyperplasia of the endometrium (Fig. 2).

The grossly irregular bleeding pattern continued, composed of lengthy periods of amenorrhea alternating with episodes of profuse vaginal bleeding lasting 3 to 4 months. At age 18 the bleeding again required hospitalization during which a hematologist ruled out any intrinsic defect in the bleeding or clotting mechanisms.

Cyclic therapy with both estrogens and progesterone was begun and continued with varying degrees of success for 3 years, until the age of 21 by which time the patient had married. In spite of the above therapy, the patient's menses were never really regulated. She finally had to be admitted to the hospital after 4 days of massive vaginal bleeding. The pelvic findings were described as being within normal limits; however, neither ovary could be palpated. Following therapy with conjugated equine estrogens, bleeding was sufficiently controlled to permit discharge from the hospital. The estrogens were continued on an intermittent basis for approximately one year, after which, at the age of 22, she voluntarily discontinued therapy. The bleeding pattern was "normal" for some 3 months, when a lengthy period of amenorrhea occurred. She was subsequently admitted to the hospital with profuse vaginal bleeding. Pelvic examination revealed a uterus the size of an 8 to 10 weeks' pregnancy; the cervix was found to be dilated, and what was thought to be placental tissue protruded from the cervical os. So much tissue was obtained by curettage that the surgeons thought clinically they were dealing with products of conception. The pathologist's report, as illustrated by Fig. 3, therefore came as a surprise; the actual tissue report read, "Somewhat atypical adenomatous polypoid hyperplasia. Should be followed."

After discharge from the hospital, the patient remained amenorrheic for 6 months and was, therefore, admitted to the hospital for diagnostic studies. It was then that the patient, now 23 years of age, first came under the care of the senior author. Pneu-



Fig. 3.

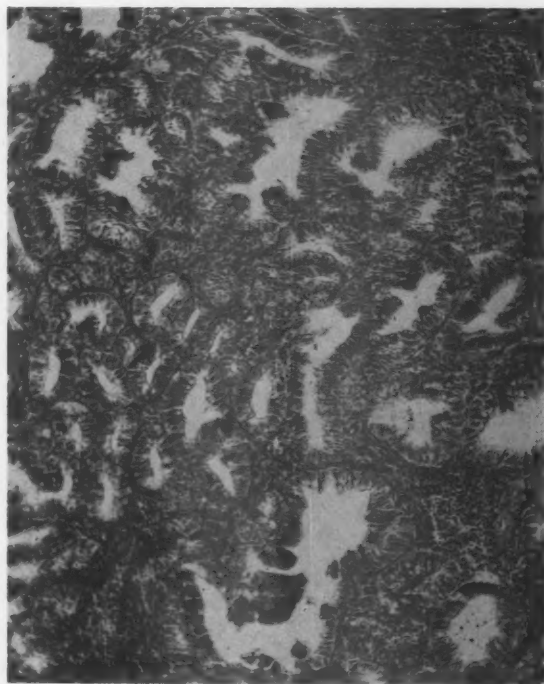


Fig. 4.

moperitoneography with nitrous oxide illustrated a uterus and ovaries of normal size. Findings on pelvic and physical examinations were normal except for moderate obesity, mild increase in hair distribution about face and extremities, and complete atrophy of the left breast. A tentative diagnosis of Stein-Leventhal syndrome was entertained, and plans were made for readmission of the patient for an examination under anesthesia and dilatation and curettage. Culdoscopy and possible exploratory laparotomy were planned if the curettings were not malignant. At the time of readmission she had been amenorrheic for a total of 8 months.

The above-mentioned procedures were carried out with the thought in mind that if the patient did not respond the studies would be an excellent basis for future comparison. The examination under anesthesia revealed a marital outlet with normal Skene and Bartholin glands; the vagina was without abnormality; the cervix was nulliparous, conical, and without erosion; the uterus was anterior, small, and mobile; the adnexa were described as containing small mobile ovaries approximately 2.0 cm. in diameter. Dila-

tation and curettage revealed abundant purplish, hemorrhagic curettings. Frozen section was done on the curettings—the pathologist's report was "Benign curettings." Culdoscopy revealed small, pale, smooth glistening, white ovaries. On the right ovary a small, yellowish dimple could be made out. Exploratory laparotomy was performed and the culdoscopic findings were confirmed. The remainder of the pelvic organs were found to be normal. A bilateral wedge resection of the ovaries was done. When incised, the ovaries were found to be firm, and immediately beneath the capsule there were numerous small 3 to 8 mm. cysts which when cut spurted a clear, slightly yellow fluid. The previously noted dimple proved to be only a small cyst. Following this wedge resection, the patient had an uncomplicated postoperative course. The pathologist reported atypical glandular hyperplasia of the endometrium (Fig. 4) and simple physiologic ovarian cysts (Fig. 5). The endometrium was further described as one which if it were not already malignant was probably at least premalignant.

Following discharge from the hospital, the

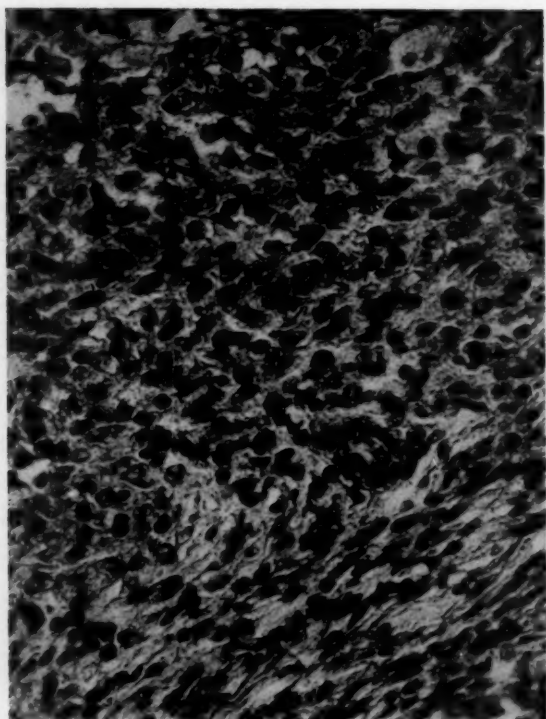


Fig. 5.



Fig. 6.

patient continued to have abnormal vaginal bleeding. Endometrial biopsy performed in November, 1958, approximately 5 months after the wedge resection, was reported as revealing endometrial carcinoma in situ (Fig. 6). Later biopsies early in 1959 confirmed this.

Therefore, in June, 1959, at the age of 24 years, the patient was admitted to the hospital with a diagnosis of endometrial carcinoma. A panhysterectomy and bilateral salpingo-oophorectomy were performed. Again she had an uneventful postoperative course and was discharged in good condition. Tissue studies showed adenocarcinoma of the endometrium without evidence of invasion, and perioophoritis (Figs. 7 and 8).

Comment

A case of noninvasive but diffuse endometrial adenocarcinoma in a 24-year-old woman with 10 years of alternating episodes of amenorrhea and vaginal bleeding is presented. A retrospective review of the histopathology reveals more abnormality than was originally suspected.

Age 15. The first tissue obtained showed a perfectly benign hyperplasia of the glands, stroma, blood vessels, and lymphoid structure. There were characteristic thrombi noted in the spiral arterioles. No hint was given of what was to appear 10 years later. (Fig. 1.)

Age 17. The second curettage produced endometrium showing a considerably different pattern. There were areas identical with those seen 2 years earlier, while other areas showed manifest Swiss-cheese hyperplasia. Last, there were focal areas of unusually packed glands with pale-staining cytoplasm and piled-up cells associated with an almost total absence of intervening stroma in these areas. If this tissue were seen in an older person it might well be called carcinoma in situ. (Fig. 2.)

Age 23. Six years after the previous curettings, extreme hyperplasia with massively dilated glands in areas showing vascular as well as stromal proliferation was seen, but there was still present an orderly glandular, stromal, and vascular relationship except in focal areas where there was atypism of cells as well as packing and piling-up in the glands. The staining of these latter areas was more intense, and the nuclei were slightly irregular and similarly hyperchromatic. (Fig. 3.)

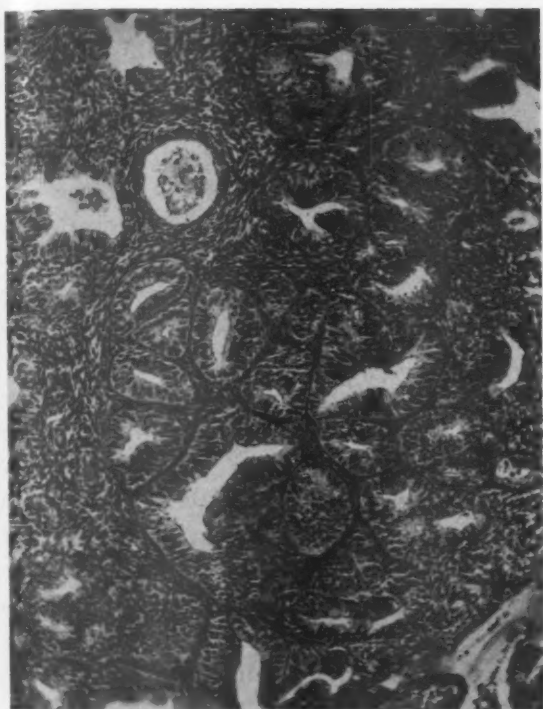


Fig. 7.

Age 23. Six months later; curettings obtained at the time of ovarian wedge resection demonstrated areas of typical hyperplasia and more numerous areas of severe atypism and packing of glands with loss of intervening stroma. Changes were probably sufficient to be consistent with early adenocarcinoma. (Fig. 4.) Wedge sections of the ovaries showed marked departure from the normal architecture. Primordial follicles were practically nonexistent, while a few burned-out microfollicular cysts and a rare follicular cyst were present. Unusually massive areas of theca interna were seen infiltrating the ovarian stroma, much of which was hyperplastic and in a few areas showed thecosis not related to any follicular apparatus. (Fig. 5.)

Age 24. Curettage specimen 6 months after wedge resection showed no improvement in the endometrium. There was benign endometrial hyperplasia interspersed with areas of undoubted adenocarcinoma. Occasionally in the center of the hyperplasia were isolated neoplastic glands. (Fig. 6.)

Age 24. Sections of endomyometrium from the specimen taken at hysterectomy, one year after the previous operation, showed an intact endometrium with widely separated areas of typical hyperplasia and the expected vascular and



Fig. 8.

stromal changes. The major portion of the endometrium was frankly neoplastic, in some areas fairly well advanced, but in no place truly invasive. Some basilar glands were almost Swiss-cheese in appearance. An interesting finding was the presence of an occasional rather enormously dilated gland filled with a solid sheet of pale pink-staining epithelial masses. Some of the nuclei when sufficiently well preserved showed abnormal mitotic figures. (Fig. 7.) Sections of the ovaries accompanying the hysterectomy specimen illustrated the expected old perioophoritis along the line of the previous wedge resection. The tunica albuginea was not unusually thick. There was but a single primordial follicle in the sections studied, contrasting with the biopsy of one year earlier in which none were seen. The ovaries showed numerous small follicular cysts with healthier appearing granulosa and considerably less theca interna. In general there was a slightly less abnormal over-all architecture. There was a total absence of corpora lutea, recent or old, and no areas of stromal hyperplasia were apparent. (Fig. 8.)

As the changing endometrial pattern in this young girl is traced from its early simple endometrial hyperplasia to a diffuse re-

placement by neoplastic elements, it is plausible that there has been some interference with the normal pituitary-ovarian relationship. This picture of hyperestrinism is typical also of the so-called Stein-Leventhal syndrome. The hyperthecosis in the ovaries of the patient parallels the changes seen in the Stein-Leventhal syndrome except for the absence of massive follicle cystosis. In this case as in the Stein-Leventhal syndrome, there is certainly hyperestrinism, failure of ovulation, and hence failure of those processes dependent upon progesterone. Others^{8, 9} have pointed out the apparent endocrine factors in common between Stein-Leventhal syndrome and endometrial carcinoma, relating the unopposed high estrogen stimulation of the endometrium to each.³

In the Stein-Leventhal syndrome the etiology is obscured somewhere in the pituitary-ovarian axis while in this case the interference might well be located in the substance of the ovary, particularly as the ovary shows almost complete absence of primordial follicles. In searching for a possible predisposing factor for the progressive endometrial changes described, the effects of early radiation must be considered. As more knowledge is gained about the widespread effects of radiation, especially in relation to the importance of "scatter doses," it becomes urgent to weigh the over-all body effect of intensive radiation. In this patient it was sufficient to cause complete destruction of the left breast. In Novak and Woodruff's discussion¹⁰ of the incidence of pelvic malignancy following radiation, they point out that the most potentially damaging effects occur not in the primary target area, "but in the adjacent areas where a sub-clinical radiation effect may manifest itself in a disturbance of cellular physiology or enzyme system sufficient to stimulate a new or altered growth." It does not take much imagination to visualize the closeness of the ovaries in a pubescent girl to the primary radiation target of the left breast, possibly helping to explain the almost total lack of primordial follicles. The small (2 to 3 cm.)

ovaries are not consistent with the oyster-like appearance of the typical Stein-Leventhal ovary; neither was there the expected thickening of the tunica albuginea. Nevertheless, there was certainly obvious lack of inhibition of the continuous luteotrophic stimulation of the ovary. This probably set the stage in a genetically predisposed individual for continuous unopposed estrogen stimulation to chronologically telescope the endometrial changes, until finally the histologic picture of true endometrial cancer was reached.

The less radical departure from the normal ovarian architecture seen after wedge resection would provoke speculation that had this procedure been done much earlier the ultimate outcome might have been altered. In retrospect, analysis of the earlier endometrial slides, even at the age of 17, indicates the die already to have been cast. In the light of this case and others now under study, much more consideration should be given to the young girl with persistent menstrual abnormalities and hyperplasia. The recently introduced potent progestational agents, if employed over a long period of time in a cyclic fashion, might well alter the outcome in cases like this.

Conclusion

A planned study involving a 24-year-old patient with adenocarcinoma of the endometrium is presented with both endometrial and ovarian biopsy material tracing the progress of the disease during a 10 year period of bleeding abnormality. In addition, an attempt is made to relate the onset of the disease to a large dosage of external radiation given shortly after the menarche. The relationship between Stein-Leventhal syndrome and endometrial cancer is discussed, and the anatomic and physiologic differences and similarities are pointed out. A plea is entered for earlier recognition of the fact that persistent menstrual abnormalities may have serious potentialities in young women, and hope is expressed that the newer, more powerful progestational agents may alter the outcome.

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Endometrial cancer, obesity, and estrogenic excretion in women

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THERE has been for many years the feeling among gynecologists and gynecological pathologists that in some way estrogens play an etiological role in the tumorigenesis of carcinoma of the endometrium. This impression is based on many pieces of evidence, so numerous and often so vague that it would be impractical to give them in detail here. It will suffice to note the more convincing in brief form.

In 1922 Schroeder¹ was the first to report the association of a carcinoma of the endometrium with an actively secreting estrogen-producing granulosa cell tumor. Many more have been reported since then so that Diddle² was able to collect 73 from the literature in 1951. Larson,³ from a study of the histories of 919 women with granulosa and theca cell tumors, concluded that 10.3 per cent of women with such tumors after the menopause develop carcinoma of the endometrium.

Carcinoma of the endometrium is frequently preceded by cystic glandular hyperplasia, a condition known to be caused by

prolonged estrogenic stimulation. Hertig and Sommers⁴ found this picture in half the cases they studied where specimens of endometrium taken several years before the appearance of carcinoma were available. The evidence seemed to indicate that this hyperplasia of the endometrium was most apt to appear from 6 to 13 years before frank carcinoma was found.

It is well known that as a woman approaches the menopause she tends more and more to have anovulatory cycles in which the endometrium is stimulated by estrogens only, no corpus luteum being formed. The pattern of cystic glandular hyperplasia is common in curettings done for menometrorrhagia at the time of the menopause. In the past, such patients often received radium therapy to stop ovarian function at the time of diagnostic curettage. Randall⁵ found cancer of the endometrium three and one-half times more often among patients whose menopauses had been characterized by bleeding than among those whose menses had stopped abruptly or tapered off gradually. Corscaden, Fertig, and Gusberg,⁶ following 958 patients who had undergone a radiotherapeutic menopause, found 15 uterine cancers—again about three times the expected incidence.

It has been noted⁷ that the menopause occurs later in women with carcinoma of the corpus than it does in women in general, 53 compared with 48, suggesting a prolonga-

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tion of estrogenic stimulation in such patients.

Failure to ovulate and prolonged sub-threshold stimulation of the endometrium are characteristic of the Stein-Leventhal syndrome, where the primary defect appears to be a mechanical interference with rupture of the Graafian follicle by a sclerotic ovarian capsule. Such patients menstruate promptly when treated with progesterone, demonstrating a chronic priming of the endometrium by their own ovarian estrogens. It seems exceedingly significant, therefore, that cancer of the endometrium occurs with much more than the expected frequency in this disease. Jackson and Dockerty⁸ found 17 carcinomas among 45 such patients.

Finally, cancer of the endometrium can be produced experimentally in rabbits either by repeated injections of stilbestrol, as was done by Meissner, Sommers, and Sherman,⁹ who reported 6 carcinomas in 18 animals so treated, or by cirrhosis of the liver and failure of the detoxifying and excretory mechanisms as described by Greene and Saxton.¹⁰ Numerous authors have described patients who developed corpus cancer apparently as a result of prolonged excessive administration of estrogens. Such cases are impressive and convincing to the doctor who sees them occur, but, being uncontrolled, they usually do not impress unduly the critical reader.

A second observation that has been recorded repeatedly is that patients with carcinoma of the endometrium tend to be overweight or even obese. Moss¹¹ studied this characteristic with care and remarks that these patients are what he calls, "lateral build, heavyweight type." The average weight of the patients he studied was 187 pounds. Corscaden¹² illustrates the typical appearance of such people in his book and mentions studies by others. His patients averaged 158 pounds in weight or 18 pounds more than the average weight of 348 patients with cancers of the cervix.

Given these two observations: the apparent causal relationship of estrogens to cancer of the corpus and the frequent

obesity which patients with this disease show, we have puzzled for years over how the two might be related. There is no evidence that chronic estrogen stimulation causes obesity. We have treated menopausal patients with pellets of estradiol which have been active steadily for 5 to 6 months and observed no gain in weight—in fact, often a loss—as a result. While in the past obesity has been thought often to be a stigma of endocrine imbalance, at present one gets the impression more and more that most authorities attach no endocrinological significance to obesity per se.

In May, 1958, Davis and Plotz¹³ presented their studies on the metabolism of progesterone-4-C¹⁴ and the same hormone labeled at position 21. The total amount of radioactivity which could be recovered in the urine, feces, and expired air totaled only 70 per cent. They assumed that the remaining 30 per cent was dissolved in and stored in the body fat. To prove this, they injected 3 pregnant and 4 nonpregnant women with radioactive progesterone before they were scheduled for some sort of abdominal operation. From 12 to 68 hours later, they removed during laparotomy some of the body fat and assayed it for radioactivity. By measurement and calculation they found 11 to 45.7 per cent in the fat, the largest amount being 19½ hours after injection.

In the normal woman, estrogenic production is intermittent, as indicated by studies of urinary excretion rates, which show two peaks, one in midcycle and the

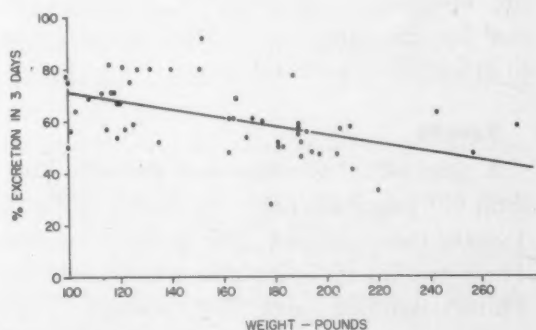


Fig. 1. Percentage of C¹⁴-labeled estradiol excreted in a 3 day period in 52 women in relation to their weights.

other at about the twenty-first day. It occurred to us that if estrogens, like progesterone, were soluble in fat, these peaks might well be smoothed out by absorption. One can conceive quite easily of a state of chronic low grade estrogen stimulation in a patient who is obese, each peak of estrogen production by such a patient's ovaries being minimized and blunted by absorption in the fat and each low level being raised and filled by release of estrogen from the fat. Such a concept would consider obesity not the result of endocrine imbalance but the cause of prolonged low level estrogen response.

While such a hypothesis is not capable of direct testing, it is possible to determine whether or not injected radioactive estradiol is excreted in the same proportion by fat and thin women and whether appreciable amounts of radioactivity can be recovered from the fat after injection.

Methods and material

Estradiol-17 β -16-C¹⁴ (6.1 μ c per milligram) was dissolved in propylene glycol in such proportion that each 400 mg. of the solvent contained 0.5 mg. of the sterol. This in our flow-gas counter will give approximately 4,500,000 c.p.m. The radioactive estrogen was injected intramuscularly into the gluteus muscle. Each patient made her own 72 hour collection. No preservative was used. Total counts on a suitable aliquot were made and corrected for self-absorption. No attempt was made to fractionate the urine. We have done so many studies on the metabolites of estradiol, estrone, etc., that for this study we confined our attention to gross excretion rates alone.

Results

A total of 52 women were studied. Their total C¹⁴ excretion rates are shown in Fig. 1. Twenty-two weighed 150 pounds or less. Their median excretion rate was 68 per cent. Thirty weighed over 150 pounds. Their median excretion rate was 56 per cent. The difference is statistically significant ($\chi^2 = 6.38$; figures significant at the 5 per cent

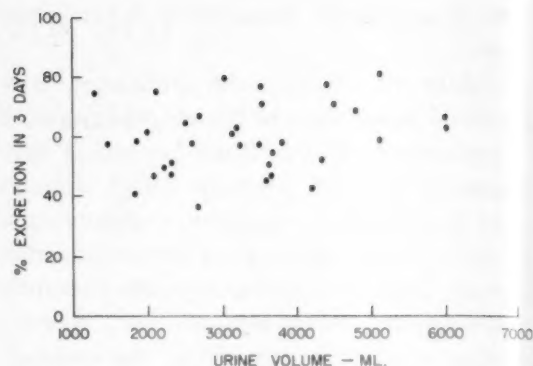


Fig. 2. Percentage of C¹⁴-labeled estradiol excreted in a 3 day period in relation to 72 hour urine volume.

level). The average excretion rate in each group is the same as the median, 68 per cent and 56 per cent. There was no correlation between total amount of the 72 hour urine specimen and total C¹⁴ excretion (Fig. 2). Analysis of the figures for changes due to age or due to the day of the cycle showed no relationship.

Storage of labeled estrogens in fat. Two experiments remain to be described:

The first woman was a patient of 45 who suffered from multiple fibromyomas. She was 5 feet tall and weighed 146 pounds. She was given an injection of 0.8 mg. of estradiol-17 β -16-C¹⁴. This material contained 5 μ c or 7,460,000 c.p.m. in our Q-gas counter. Eighteen hours later at the close of the operation (hysterectomy) for the fibromyomas, 70 grams of fat was removed from the abdominal wall. This fat was extracted and found to contain 8,346 c.p.m. per pound.

The second patient was a 58-year-old woman who was suffering from a recurrent carcinoma of the endometrium. She was 5 feet tall and weighed 200 pounds. She received 1 mg. of estradiol-17 β -16-C¹⁴ intramuscularly. This is 6.1 μ c or 9,300,000 c.p.m. Fifteen hours later, after an exploratory laparotomy, 91 grams of fat was removed from the margins of the abdominal wound before closure. This fat was found to contain 9,300 c.p.m. per pound. Assuming that a normal weight for a 5 foot woman is 100 pounds, this patient must have had about 100 pounds of fat. If all the fat was equally radioactive, she was storing 10 per cent of the injected dose.

The fat was extracted by grinding it in a Waring Blendor with four times its weight of ethanol. The mixture was centrifuged and the residue extracted with two times its weight of 80 per cent ethanol. After a second centrifugation, the residue was extracted twice with a 1:1 mixture of ethanol and acetone. All supernatants were combined and concentrated under vacuum until all solvent had been removed and only the semiliquid fat was left. The fat and extracted steroids were diluted with 300 c.c. of petroleum ether. The mixture was extracted with 80 per cent ethanol which was concentrated and counted. From the ethanol fraction a partition was made between water and ether, each fraction being counted again. Two thirds of the radioactivity was found in the ether fraction.

All this procedure constitutes a method of attempting to separate the radioactive materials from the unworkable fat. The fact that two thirds of the radioactivity was found in ether-soluble form suggests that fat absorbs estradiol-17 β in its free unconjugated form and not particularly readily as the water-soluble glucuronides and sulfates.

Comment

It would be ridiculous to assume that we have proved that naturally produced estrogens are stored in the body fat and that therefore a fat person will excrete lower peaks of active estrogens than a thin one and will be continuously stimulated by her own estrogens. This is the speculation which led to the above experiment. The fact that

fat women seem to excrete less radioactivity in 72 hours when injected with C¹⁴-labeled estradiol than do thin ones and that in two women appreciable radioactivity was found in the fat 15 and 18 hours after intramuscular injection is consistent with this theory and may stimulate us and others to more critical experiments. Perhaps of particular interest would be the extraction and biological assay of fat from a patient with a functioning granulosa cell or theca cell tumor. The estrogen content of fat in persons with cystic glandular hyperplasia might also be of interest.

Summary

Fifty-two women were injected with estradiol-17 β -16-C¹⁴ and the radioactivity of their urine determined at 72 hours. They excreted 28 to 92 per cent. Twenty-two women weighing 150 pounds or less excreted an average of 68 per cent of the injected radioactive carbon in 72 hours. Thirty obese women, 150 to 240 pounds in weight, excreted an average of 56 per cent in 72 hours. There seemed to be a statistically significant correlation between weight and percentage excretion; the thinner the patient, the higher the rate of excretion. In 2 patients, 15 and 18 hours after intramuscular injection, considerable quantities of radioactivity were found in the fat.

The theory is propounded that cancer of the endometrium, if it is due to chronic estrogenic stimulation, may occur in obese women frequently because these individuals store estrogens in their fat and possibly thereby prolong the effect of their own hormones on their own endometria.

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Physiologic control of conception with norethynodrel

Clinical experience

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PHYSIOLOGIC control of fertility by administration of hormonal agents became available as early as 1921 when Haberlandt showed that the transplantation of ovaries from pregnant laboratory animals into mature females of the same species caused the latter to be sterile for limited periods. This effect was ascribed to the presence of corpus luteum hormone in the transplanted ovaries. Similar research, and subsequent identification of the steroid hormone progesterone as the active biologic principle elaborated by the corpus luteum, demonstrated the inhibitory activity of progesterone on ovulation. Other investigators have demonstrated a similar biologic effect with both estrogen and testosterone. Suppression of ovulation with the three hormones is effected by the suppression or inhibition of the secretion of the pituitary gonadotropins. Prolonged therapy with these steroids for contraceptive purposes is not feasible for many reasons which include several undesirable side effects: the androgenic effects of testosterone, the gastrointestinal, dermal, and breast changes associated with prolonged estrogen therapy, and the unacceptability of parenteral progesterone. Oral progesterone has not been satisfactory because (1) large daily

doses (300 mg.) are necessary to approach reliable inhibition and (2) the occurrence of shortened menstrual cycles, i.e., breakthrough bleeding which occurs in a significant percentage of patients.

Within recent years, many new compounds similar to progesterone in structure and biologic activity have been prepared and made available. We are seeing the advent of an era marked with striking success in the synthesis of steroidal derivatives which are not only more potent in some respects than the naturally occurring hormones but which retain the favorable biologic actions with a minimum of undesirable side effects. A large number of these compounds have been synthesized and studied by different investigators but only a few are currently available for clinical application.

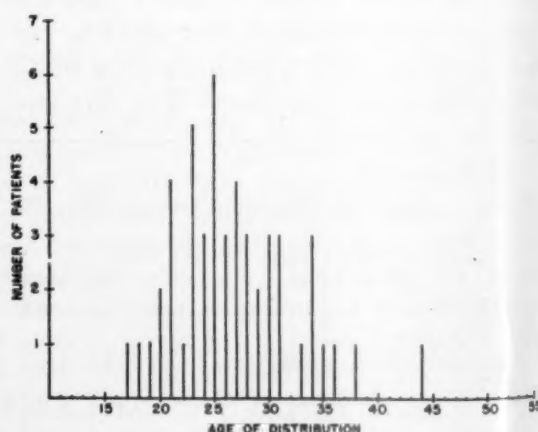


Fig. 1.

From the Walston Army Hospital.

The views and opinions expressed herein do not necessarily represent those of the Surgeon General or the Department of the Army.

Two of these, 17 alpha-ethinyl-19-nortestosterones* and 17 alpha-ethinyl-(5,10)-estraeone† are clinically effective when ingested. Extensive clinical research and application has been reported with these steroids in a variety of obstetric and gynecologic conditions. It was apparent that the oral ingestion of either steroid effectively inhibited ovulation at low dosages and the incidence of metabolic and biologic contraindications was negligible.

The intermediate metabolic pathways of both compounds has not yet been elucidated. Clinical studies suggest that the compounds are altered or metabolized in the body to produce the progestational effect. Interestingly enough, norethynodrel‡ has an inherent estrogenic effect, and the clinical effectiveness of this compound has been further enhanced by the addition of 1.5 per cent of the 3-methyl ether of ethynylestradiol (EMEE).

Material and methods

Selection of patients. All 50 patients selected from the Obstetric and Gynecologic Clinic, Fitzsimons Army Hospital, during the period March 1, 1958, to April 1, 1959, had specifically requested instruction in contraceptive techniques. While the use of a diaphragm with spermicidal jelly is usually recommended, this particular group of 50 patients was selected over a 14 months' period as suitable candidates for hormonal inhibition of ovulation with 19-norethynodrel. Initially, the only patients selected were those who fulfilled the following criteria: (a) a proved fertility index (para iii or greater); (b) a recent failure with other contraceptive techniques.

These patients were individually interviewed and carefully appraised of the experimental and voluntary features of the study. Pertinent data concerning their sexual mores, and menstrual, obstetric, and gynecologic history was obtained before

Table I. Contraceptive history

Method	No. of patients	Success	Failure
Mechanical-chemical	26	10	16
Rhythm only	9		9
No method	15		

therapy. Subsequently, eligibility in the study was extended though limited to fertile married candidates desiring contraceptive advice. In 7 instances, contraception was "indicated" for the following reasons: proved cervical incompetency, 2; chronic abortion, 1; extensive pulmonary disease, 2; severe varicosities, 1; preoperative candidate, immediate post partum, 1. In the remaining 43 patients the hormonal technique was elective.

The age distribution extends from 17 to 44 years (Fig. 1). All but 2 were white. Fifty-four per cent were para iii or more. In one instance, therapy was started shortly after marriage in a young, presumably fertile nulligravida. The menstrual history of 14 patients was atypical with either menometrorrhagia or extended periods of functional amenorrhea. Other investigators have shown that failure to maintain a temporal cycle relationship often implies anovulatory cycles. This possibility was recognized. However, these patients had recently conceived, and histologic evidence of ovulation was obtained before therapy was started.

Various contraceptive techniques (Table I) were used by 70 per cent of the group. Success with the rhythm method had been uniformly poor; the average parity in this group of 9 patients was 4. However, 4 of these patients were among the group of 14 with irregular cycles, and 3 others had conceived at least twice in the amenorrheic postpartum interval after lactation. Surprisingly poor results were obtained with the mechanical-chemical techniques of contraception. A 38 per cent effectiveness is significantly lower than the usual 50 to 80 per cent values reported. This reflects only our tendency to select highly fertile patients, dissatisfied with the diaphragm, con-

*Nolutin, marketed by Parke, Davis & Company.

†Enovid, G. D. Searle & Co. (norethynodrel with 1.5 per cent ethynylestradiol-3-methyl ether).

Table II. Biopsy schedule

Patient	Base line	Cycle 1	Cycle 4	Cycle 7	Cycle 8 (no drug)	Cycle 9	Cycle 12
1		X					
3		X					
8		*	X	X			
9		X	X	X	X	5 biopsies	
10	X						
11	X		X				
12		†	X				
13		X					
14		X					
15	X						
16		X					
21	X	X					
22		X					
23	X	X	X	X	X		
24		X	X				
25	X	X	X	X			
26	X			X			
27		X	X	X			X
28	X		X	X			
29	X	X					
30			X				
31	X	X	X				
32	X	X	X				
33		X					
34		X	X				
35		X	X	X			
36	X	X	X				
37		X	X				
39		X					
40	X	X					
41	X	X					
42			X				
43		†					
44		X					

*Forty-five-day acyclic treatment

†Post partum, no menses.

dom, or jellies because of an apparent recent failure with the method.

Procedure. After the initial interview, 36 of the 50 patients were given one vial containing 20 tablets of 10 mg. of norethynodrel plus 1.5 per cent EMEE with instructions to take one tablet daily, beginning on Day 5 of the menstrual cycle (in 2 cases on Day 9) through Day 24. One patient in this group was started in an acyclic fashion for 45 days, then continued in the usual cyclic fashion. The remaining 14 patients were started after the 6 weeks' postpartum examination, still amenorrheic and, in 3 instances, still lactating. Pregnancy was excluded in the group before therapy was started. The only modification of the origi-

nal instructions for this group was that they abstain from intercourse until Day 5 of therapy. It is of interest that "weaning" occurred without discomfort 7 to 10 days after therapy was started, albeit unplanned.

All patients were advised to contact the clinic with the advent of their menses, and they were not to discontinue the drug without counsel. They were not appraised of the reported side effects of therapy unless specific inquiry thereof was made. No other contraceptive devices were to be used.

It is generally conceded that it may be difficult or impossible to recognize true ovulation in a normal cycle by any single index. Ovulatory type cycles were assumed to have occurred in 36 of the group with essen-

tially normal cycles, i.e., a similarity of flow and regularity within a range of 5 days and these 5 within the outer limits of 24 and 36 days. This assumption seemed valid for the entire group, but since 14 patients with irregular cycles were included, histologic proof of ovulation was obtained before therapy started. It was not feasible to study these 14 patients to further establish the constancy of ovulation.

Various investigators have reported the atypical endometrial changes effected in patients with this therapy. In order to further study these changes, a biopsy schedule was planned and accomplished in 34 patients (Table II). Most endometrial biopsies were done within 6 hours after the onset of the menses as a clinic procedure.

Analysis of results

Forty-seven of the 50 patients have been treated successfully with norethynodrel through 204 menstrual cycles (Table III) over a period of 1 to 14 months. No pregnancies have occurred in patients on therapy during this interval of time. Ten patients have just completed their first therapy cycle uneventfully, and the remaining 37 patients have had 2 cycles or more. Three patients had to be dropped from the study because of intolerable side effects; in 2 patients recurrent breakthrough bleeding persisted and in one other patient severe nausea and vomiting complicated therapy.

Table III. Extent of therapy

Cycle	No. of patients
1	10
2	2
3	8
4	7
5	5
6	3
7	5
8	4
9	2
10	1
Success	47
Failure	3
Total	50

Six patients have been dropped from the study after varying intervals of therapy when they left the immediate area and could not be followed. The remaining 41 continue on therapy. Adequate information on the posttreatment menstrual history has not been obtained in 2 patients. In 4 others, our experience parallels that of Pincus, Rock, and others who found that there is a significant average increase in the length of the cycle immediately following medication, often as much as 15 days. In 2 cases, the first posttreatment cycle flow was quite heavy and prolonged. Both patients bled for 10 days. Bleeding subsided spontaneously and subsequent posttreatment menses were unremarkable.

Menses usually began 3 days after the last treatment day, and the flow lasted 4 days. After the first one or two treatment cycles, most patients commented on the scanty amount of flow. We have not experienced any prolongation of the estrous cycle or the phenomenon of "silent-menstruation" reported by others. However, we advise our patients to contact the clinic if withdrawal bleeding has not occurred within 6 days after the last day of therapy. It is of interest that most patients who complained of pretherapy dysmenorrhea and premenstrual tension uniformly remarked on the absence of such symptoms while on therapy.

We have no significant experience with breakthrough bleeding and bimodal menstrual cycles which follow the omission of a number of tablets. Only 2 patients are known to have "forgotten" their medication for 2 or 3 days. In both cases, vaginal staining, not typical of the menses, ensued and was controlled by increasing the daily dosage to 30 mg. which was then tapered to 10 mg. 3 days later. Three of the 5 patients who have been on therapy for 7 cycles were studied more extensively to include PBI, 17-ketosteroids, 17-OH corticosteroids, and bleeding and clotting times. Our findings are of no statistical significance and are of interest only in that essentially normal values were obtained.

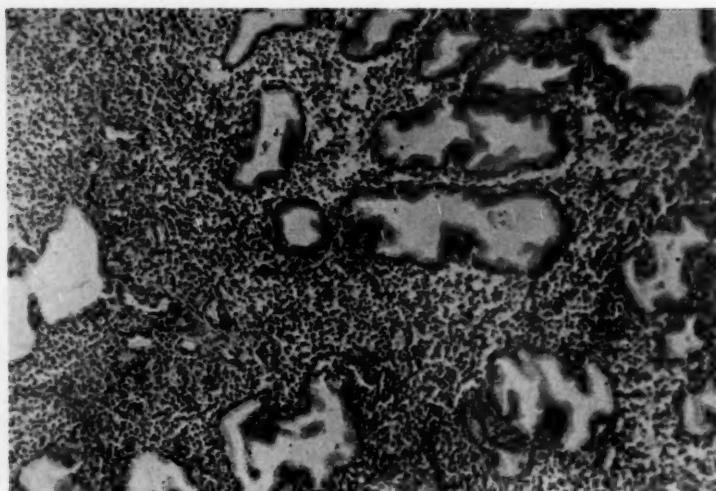


Fig. 2. Late secretory endometrium, pretherapy.

Side effects

The number of patients who reported untoward symptoms is small. Three patients were dropped from the study as noted previously. The trend in side effects parallels that reported by other investigators.

Gastrointestinal symptoms. These were usually anorexia, malaise, and a vague "empty feeling." Emesis was rare. These symptoms were transient, rarely lasted more than the first 10 treatment days of Cycle 1 and did not recur in subsequent cycles. In only one patient did these symptoms require discontinuing the drug.

A slight tendency to weight gain. Weight gain was usually 5 to 8 pounds in about

one fifth of the patients. Some decrease in this weight occurred during the first few days of flow, and this may represent some water retention.

Breakthrough bleeding. This was usually spotting, which can be controlled by increasing the daily dosage to 30 mg. for 3 days and then reducing the dosage to 10 mg. as initially programmed.

Miscellaneous. Various other less well-defined effects include transient mastalgia, neuromuscular irritability, headaches, and diarrhea.

We have not noted any significant effect on the libido. Many patients in this series now practice coitus more frequently which

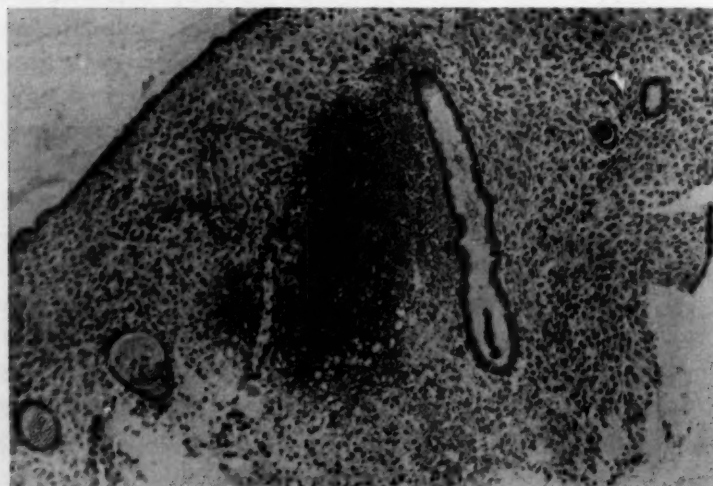
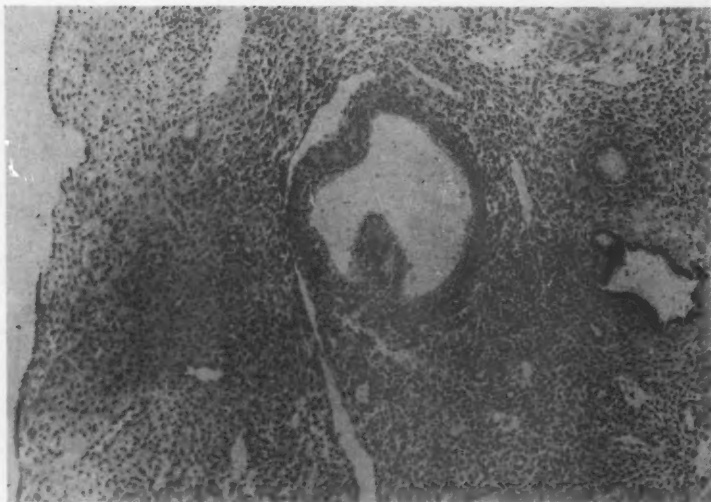


Fig. 3. Cycle 1, early menstrual, usual dosage. Glandular inactivity is apparent and "out of phase" in contrast to the stromal decidual transformation and edema.

Fig. 4. Cycle 4, early menstrual, usual dosage. Note the accentuated periglandular stromal "halo," decidual transformation, and edema.



probably reflects only confidence in the drug as a contraceptive device.

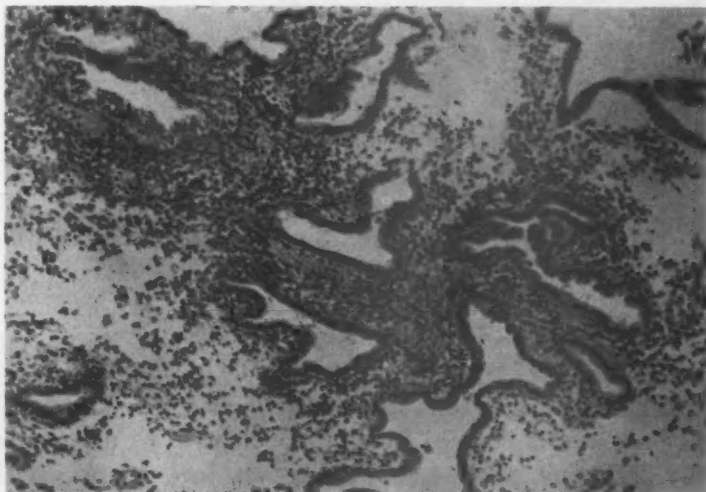
Details of endometrial response to medication

In the main, our experience with the histologic alterations effected by the progestational compounds on the endometrium parallels that reported by other investigators. The effects of the drug cannot be classified according to conventional standards and the changes in each of the components of the endometrium must be described. Our pathologists label the endometrial picture merely as "norethynodrel effect," which is adequate enough for those familiar with

the consistent atypia evident. Despite the variations evident in different portions of the same endometrium, these fragments ordinarily give a true picture of the over-all condition of the responsive portion of the endometrium, albeit they may reflect only an isolated atypical portion. We have never found a biopsy specimen which showed a completely typical secretory endometrium at a time in the treated cycle when it might be expected. In none of the specimens could a positive diagnosis for ovulation be made after 20 days of therapy as outlined.

Four different components of the endometrium were observed individually, namely, the glands, epithelium, blood vessels, and

Fig. 5. Cycle 8, early menstrual, no therapy after 7 previous consecutive medication cycles. The late secretory pattern is evident.



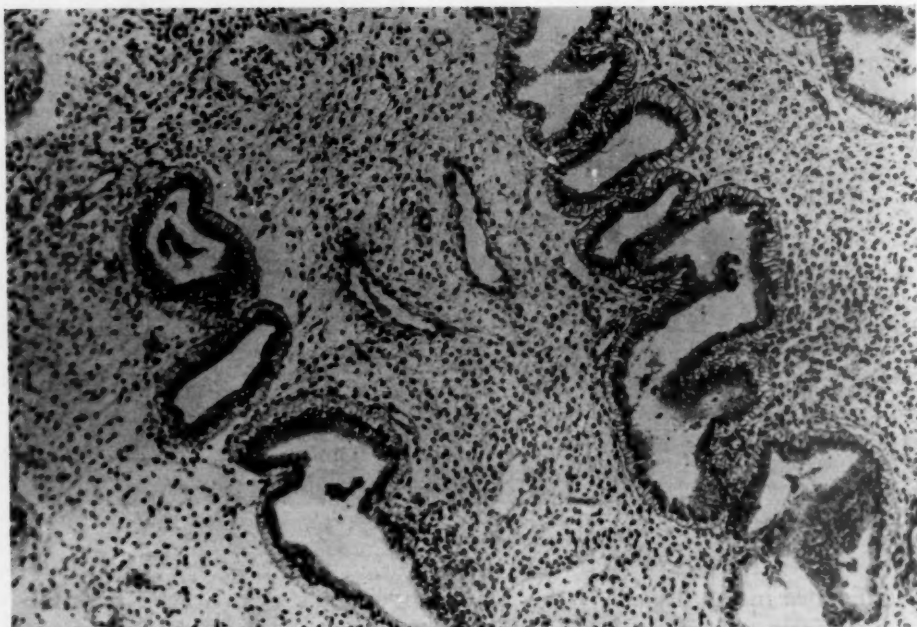


Fig. 6. Cycle 9, Day 10 (Day 5 of therapy). The glandular pattern is suggestive of the usual fifth postovulatory day and is referred to as "19 day" glands. Stromal edema is apparent but predecidual cytoplasmic enlargement is absent.

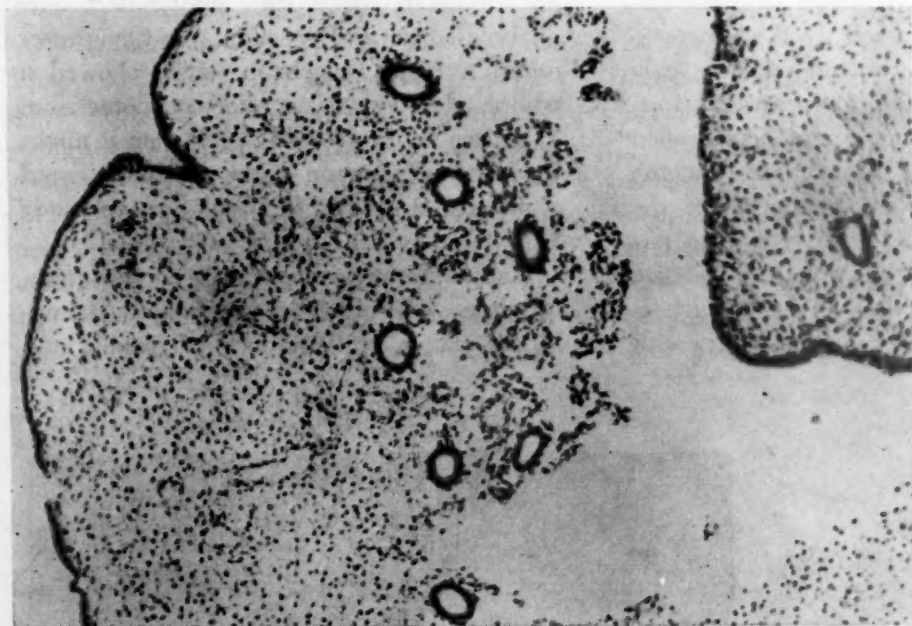


Fig. 7. Cycle 9, Day 15 (Day 10 of therapy). The regressive changes in glandular and epithelial pattern are dramatic. Stromal edema persists, but the cellular pattern is unchanged.

stroma. The initial impression was that the glands and blood vessels were "arrested" in the proliferative phase while the epithelial cells and stroma showed progestational activity following norethynodrel therapy. In

some a mixed type of endometrium was observed. Figs. 2 through 9 illustrate the more striking effects of norethynodrel on the endometrium. More recently, Pincus and associates^{9, 10} and Garcia and co-work-

ers⁸ have described glandular regression rather than arrest. Serial biopsies illustrate an interesting time differential in the development of endometrial glandular epithelium between normal and medicated women. The immediate so-called secretory response in the glands is short lived (Fig. 5). With continued medication, the response rarely, and only in a few glands here and there, progresses to the actual secretion into the lumen characteristic of the seventh day after ovulation. The glands themselves do not increase in size nor do they change in shape. Instead, they give the appearance of gradual regression.

In general, the endometrial pattern is essentially the same in all patients irrespective of when the drug was started or in what dosage after 20 days of therapy. Serial biopsies suggest that the material (or its metabolites) imposes a sequence of endometrial change which is repeated cycle after cycle. Alterations in glycogen, alkaline phosphatase, and lipid distribution have been reported, and are now under study.

Comment and conclusions

Population control in one form or another has been a universal aim, whether people have always been conscious of it or not. The desire for, as distinct from the achievement of, this goal has been characteristic of many societies widely removed in time and place. In earlier centuries, the perils and difficulties of day-to-day life, epidemic and endemic disease, and man's inhumanity to man limited the population density. However, in the last 200 years, man has propagated himself so rapidly that if the increase continues at the present rate for another 1,000 years, there may not be enough standing room on earth. The physical resources of our world seem finite, but man's reproductive potential at least is theoretically almost infinite.

Definite progress in control techniques has been made in the last century. Birth control as such is no longer receiving significant opposition in America. While use of the diaphragm, condom, and spermicidal jellies re-

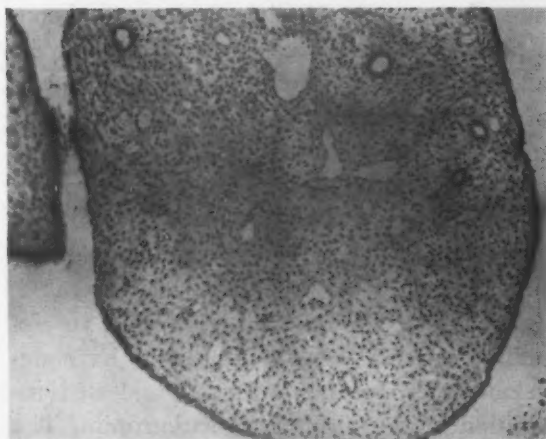


Fig. 8. Cycle 9, Day 20 (Day 15 of therapy). The glandular and epithelial inactivity persists. The stromal edema is subsiding and an early predecidual cytoplasmic transformation is apparent.

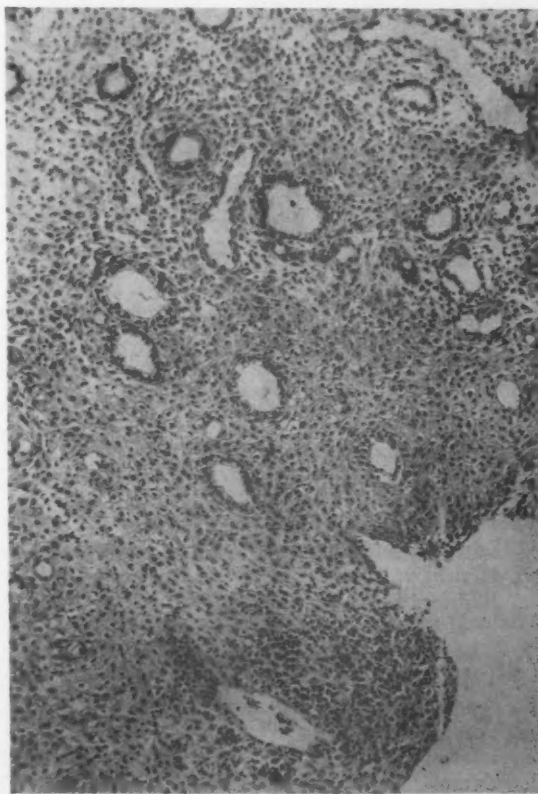


Fig. 9. Cycle 9, Day 26 (Day 21 of therapy). The predecidual change in the cytoplasmic cells has increased. The glandular epithelium reflects an increase in activity with minimal spiralization.

mains the most effective and currently the most popular methods for the great mass of people, recent success with the synthetic progestins has opened an entirely new ave-

nue of approach. Physiologic control of conception now more than ever is possible by altering ever so slightly the delicate systems of checks and balances on which human reproduction is dependent.

Clinical experience with the progestins is rapidly accumulating in the literature. Our experience parallels that of others: the oral progestins are an effective, well-tolerated, and acceptable contraceptive agent; no significant adverse effects appear to have developed despite the apparently selected inhibition of the pituitary gonadotropins. The metabolic pathways of these compounds remains to be elaborated and the vulnerability of the reproductive system to long-term therapy discovered. Nonetheless, preliminary experience with this oral contraceptive technique suggests a major therapeutic triumph.

Summary

Clinical experience with 19-norethynodrel in 50 highly fertile patients over a 14 months' period at Fitzsimons Army Hospital is reported. The pharmacologic, meta-

bolic, and biologic effects of this highly potent oral progestational compound are reviewed. Multiple serial biopsies illustrate the peculiar histopathologic changes associated with long-term therapy. Effective contraception appears to have been obtained.

All the drugs used in this study were furnished through the courtesy of Dr. J. W. Crosson, Assistant Director, Clinical Research, G. D. Searle & Co. I am grateful to Mr. William X. Hommell, Laboratory Service, Fitzsimons Army Hospital, for both the excellent reproductions and photography, as well as Mrs. Thelma Speight and Mrs. Catherine Watson for their secretarial assistance.

Addendum. Fifty additional patients have been treated successfully since Jan. 1, 1960, at Walson Army Hospital, Fort Dix, New Jersey, through 288 menstrual cycles (24 woman-years). During this period of time no pregnancies have occurred in the group although no other contraceptive techniques have been practiced. A successful transition from the 10 mg. to the 5 mg. dose size has been made with only a transient increase in breakthrough bleeding.

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Oral contraception by norethynodrel

A 3 year field study

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IN THE many areas of the world where the standard of living is at subsistence level, each specific improvement in death control serves to depress that standard. As the living standard goes down, malnutrition grows, ill health increases, and the death rate rises. Furthermore, such low income levels leave little money available for public health activities. In these areas widespread provision of effective and acceptable methods of pregnancy spacing is essential to further health improvement. It is encouraging that statesmen in many countries are now becoming aware of this problem.

Methods of contraception have been available for years. Most of them involve some interference with the normal pattern of sexual intercourse, its prelude or postlude; others are of questionable reversibility (vasectomy and salpingectomy) or are considered dangerous (intrauterine and intra-cervical devices²). Experience has shown that contraception can be widely effective when made available to all and promoted with enthusiasm.¹¹ Yet, because of the disadvantages of present methods, the wish is commonly expressed for an oral contraceptive, preferably long lasting, and certainly easy to take.

The observation that certain western American Indians ate the leaves of *Lithospermum ruderale* to prevent conception³⁴ suggested that oral contraception might be practical. Pharmacologists found that this and related plants contain substances that inactivate pituitary gonadotropins in vitro and in vivo with failure of the gonads to develop in immature animals and reversible cessation of the estrous cycle in those already mature. Preliminary trials in humans were disappointing.^{6, 8, 10, 14, 21}

The observation by Nag¹³ that rats fed field peas (*Pisum sativum*) were less fertile stimulated Sanyal to isolate metaxylohydroquinone as the active substance. He reported that this apparently nontoxic and inexpensive substance reduced the pregnancy rate of women by 50 to 75 per cent.²⁶⁻³⁰ Such incomplete effectiveness inhibits widespread patient acceptance; the method has not gained general approval.

Antihyaluronidases are reported to be effective contraceptives when used as vaginal suppositories.⁷ Most investigations testing them by mouth have not shown any significant effect.^{15, 31} Also recently under trial are cirantin, an oil extract of orange skins,^{3, 4} and rottlerin, an extract of a Philippine milkweed.³⁷ Mode of action and clinical effectiveness are under preliminary investigation.

Progesterone in pregnancy blocks ovulation and so prevents a superimposed preg-

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nancy. Simulating this hormonal balance characteristic of pregnancy should thus be a form of contraception approximating normal physiology. Progesterone itself has been tried, but for oral use 300 mg. daily is required.¹⁶ This is expensive for general use. Several progestin-like synthetic steroids have been developed within the last 10 years. Tests by Pincus and associates show these effectively suppressed ovulation when given by mouth to animals and to women. Three of these compounds have reached commercial production: 17 α -ethinyl-19-nortestosterone,* 17 α -ethyl-19-nortestosterone,† and 17 α -ethinyl-5(10)-estraeneolone, known as norethynodrel.‡

The ideal contraceptive must be effective in preventing conception, safe for the persons using it, psychologically and economically acceptable, and reliably reversible. Although no present method is ideal on all counts, the preliminary work with norethynodrel²² suggested that it might closely approach this ideal. Therefore, in 1957 we decided to test this product in the field.

Method

Study area. A region in which population pressure is a public health problem was sought—one which has a high birth rate, low death rate, and low per capita income. Puerto Rico has a birth rate which averaged 41 per 1,000 population from 1946 to 1950 and declined to 35 by 1956. The death rate dropped steadily from 1935 to 1955 and is now between 7 and 8 per 1,000 population. The annual income per person rose rapidly in the last 10 years; it reached \$410 in 1955. That for continental United States in the same year was \$1,866. The population doubled during the last 50 years despite a net loss by migration of half a million people. The island contains 675 people for each of its 3,435 square miles, although half the land is steep and noncultivable. Popula-

Table I. Population characteristics

Number of women	550
Age range, in years	16-46
Average age	27.5
Average years married	8.7
Pregnancies (averages)	
Children now alive	4.2
Born alive but died	0.4
Stillborn	0.1
Abortions	0.5
Total pregnancies	5.2
Pregnancies per 100 married years	59
Pregnancies per 100 years of exposure*	110

*"Years of exposure" are the total years married less 10 months for each full-term delivery and 4 months for each abortion.²³ Time of living separately, though appreciable for a few families, was not enough for the whole to warrant consideration in the calculation.

tion density is comparable to the flat and fertile Ganges River Valley and the Malabar Coast of India.

Headquarters for field work was Humacao, the twelfth largest municipality in Puerto Rico, population 35,000 in 1950, and demographically typical of the island. The study was under the auspices of the Ryder Memorial Hospital. Its gynecologist and obstetrician (A. P. S.) had medical supervision of the study, made the physical examinations, and arranged for social service workers to distribute the contraceptive materials and instructions, keep records, and visit patients as necessary. The data were analyzed at the Harvard School of Public Health after field visits to organize the plan of investigation and to collect the needed details.

The population. The important features of the population studied are summarized in Table I.

The present report concerns two groups of women. Work with the R series started in April, 1957. Each family in three crowded urban areas was paid a home visit by a social worker. In the first two of these areas 1,107 persons were found living in one-story houses on 7 acres of land. This is five times the density for the city as a whole. Subsequently, one rural and one suburban area were surveyed; here poor families live on government land allotted to them for housing. All women living with their hus-

*Norlutin, marketed by Syntex and by Parke, Davis & Company.

†Nilevar, marketed by G. D. Searle and Company.

‡Enovid, marketed by G. D. Searle and Company.

bands, having at least 2 children, not then pregnant, and aged 40 years or less, were invited to use the contraceptive pills which the social worker offered to bring them, without charge, every month.

The second group, called the P series, was recruited, starting in May, 1957, from women who came to the Ryder Memorial Hospital Outpatient Clinic for contraceptive aid, met the R series requirements, and chose to try this method. Alternative methods offered were the diaphragm, vaginal jelly or foam, and condoms. Most of the early P cases were recruited from women coming for postpartum examinations; to these women contraception is regularly offered. As word spread that the pills were available, without charge other than the initial \$2 clinic registration fee, increasing numbers came specifically to secure norethynodrel.

Procedure. All women in both groups were given an initial pelvic and general physical examination. Each was provided a bottle of 20 tablets and instructed as follows:

Take one pill each day with your evening meal. Begin on the fourth day after the day on which menses start. Stop when your bottle of 20 pills is empty. Wait until your next menses and secure another bottle of pills. Start the pills again on the fifth menstrual day. If, by any chance, you do not have a period within 10 days of stopping, get a new bottle and start taking the pills that evening. If you wait longer than 10 days you may become pregnant.

If you begin to bleed while still taking the pills, take 2 pills every day until the bleeding stops, then one pill daily until the bottle is empty. If anything prevents you from getting the next bottle of pills until later than the fifth day of menstruation, start again by taking 2 pills each day for as many days as you started late, after the fifth day, then one pill every day.

Those with postpartum amenorrhea were directed to begin the pills immediately.

After their initial visit, women in the R series were given supplies each month in their homes while those of the P series were instructed to return to the hospital for further supplies when menstruation had begun. A record was made at each visit of the date of starting the tablets, the date,

character, and duration of the menses, frequency of intercourse, and any symptoms or difficulties noted during the preceding interval. Women who had used the method regularly for several months without difficulty were given 2 months' supply. Those who did not return were followed up by a personal visit from one of the social workers or by letter if they lived too far away. Care was taken to find out why they had stopped using norethynodrel but no effort was made to influence them to resume the program.

Information available in 1957²² suggested that 9.85 mg. of norethynodrel combined with 0.15 mg. of the synthetic estrin, ethynylestradiol-3-methyl ether, was the optimal daily dosage. Subsequent experience¹⁹ suggested that a smaller dose was equally effective and less apt to give certain unpleasant symptoms; therefore early in 1959 we began giving half the previous daily dose, tablets containing 5.0 mg. of norethynodrel with 0.075 mg. of ethynylestradiol-3-methyl ether.*

The first 18 months' experience of the R and P series is included in reports by Pincus and associates.²⁰ Our report is based on all recorded experience of the first 150 R cases and the first 400 P cases through February, 1960. All women using the method, plus all who had discontinued it and could be located within 20 miles of the Hospital, were interviewed beginning in November, 1959; a comprehensive questionnaire was filled out, and, on those who could come to the hospital, a pelvic and general physical examination was made (Table IV). Experience after February, 1960, will be reported subsequently.

Results

Contraceptive effectiveness. During the 518 woman-years of experience with norethynodrel accumulated by the 550 women in this study 11 pregnancies occurred. Of these, 4 had started before norethynodrel was begun. Three occurred

*The 10 mg. and 5 mg. tablets, known as Enovid, have been supplied by G. D. Searle and Company.

when the women waited more than the prescribed 10 days for the return of menses (one woman waiting 15, one 20, and one 30 days). The other 4 followed failure of the women to take the tablets daily; trustworthy details as to number and sequence of omissions could not be secured.

Tietze³³ has defined three measures of the effectiveness of contraceptive methods: *physiologic* effectiveness is that measured when a given method is used according to instructions on every occasion of need; *clinical* effectiveness when in the hands of users under actual use conditions; and *demographic* effectiveness by the reduction of the birth rate of an entire population who have been instructed in the given method and to whom materials are available whether the individuals are using them or not.

No woman who followed instructions has become pregnant during 518 woman-years of use. Norethynodrel is thus physiologically completely effective. If the 11 pregnancies are attributed to faults in the method, the pregnancy rate for all users is 2.1 conceptions per 100 years of exposure. In Puerto Rico the fertility rate is approximately constant from age 20 years to age 30, after which it decreases. Our population, married an average of 8.7 years, was aged 27.5 years at the beginning of this trial. The rate of 2.1 thus contrasts directly with their preinstruction rate of 110 pregnancies per 100 years of exposure. Preceding attempts at contraception had not affected fertility; the 176 women reporting previous experience with one or more contraceptive methods had a rate of 106 pregnancies per 100 years of exposure, while the 328 reporting no such experience had a rate of 110.

Considering the population of those who at any time tried norethynodrel one can compare the "community" preinstruction pregnancy rate of 110 pregnancies per 100 years of exposure to the postinstruction pregnancy rate for all women who could be followed up, combining active and discontinued cases, of 17 per 100 years of exposure. The rate after stopping for all women who stopped was 91 pregnancies

per 100 years of exposure. These results demonstrate that *physiological* effectiveness is complete, *clinical* effectiveness is great, and *demographic* effectiveness, though reduced by the continued fertility of those who have discontinued the method, is marked.

Dangerous or hidden side effects. No method of pregnancy spacing, even though highly effective, is justifiable if it endangers life or health. Only 2 women have died while using this method, one from burns and one from chronic hypertension with congestive heart failure. Another woman developed pulmonary tuberculosis, controlled by therapy. None of these effects could in any way be attributed to norethynodrel. Hemoglobin levels of 137 women were determined after an average of 14 months of use; these women showed an average of 10.4 ± 0.11 (standard error) Gm. per cent as compared with 10.6 ± 0.13 Gm. per cent for 79 women of comparable age (28.6 years) and parity (3.7 pregnancies) attending the Ryder Memorial Hospital Outpatient Clinic but not using norethynodrel. Blood pressure was neither raised nor lowered significantly as shown by observations on 179 users (average 13 months' use) compared with 85 controls. Biochemical studies made on 300 users by Pincus and associates¹⁸ showed no evidence of hidden toxicity after as many as 33 months of use. Psychological effects (except as described under "Unpleasant but benign side effects") have not been detected.

Popular rumor had it that this procedure caused cancer. A definitive answer is impossible within 3 years and with as small a sample as now available. Careful watch has been kept for suggestive indications, especially during the final physical examinations. During 698 woman-years of observation (518 woman-years of use and 180 woman-years of post-use experience), no signs of cancer, other than cervical, have been noted.

Cervical biopsies were taken on 40 women and were examined histologically by Rock and Garcia at the Free Hospital for Women,

Brookline, Massachusetts. Carcinoma in situ was reported once, in a woman 33 years old, after 6 months' use of norethynodrel. Eight months after this biopsy she discontinued the method. At that time and also 6 months later biopsies were negative. Lee¹² found by biopsy of 3,149 healthy Puerto Rican women that 25, or 0.79 per cent, had carcinoma in situ. After 3 years' observation without treatment none had invasive carcinoma. Other studies³⁰ showed 28 per cent invasive after 5 years and 33 per cent invasive after 9 years, without treatment.

Epidermoid carcinoma, Grade II, was found in another woman. On starting the method she had normal pelvic findings. A vaginal smear 18 months later was reported suggestive of cancer. A cervical biopsy was made after 21 months' experience, carcinoma found, norethynodrel stopped, and radiation treatment begun. To be allowed to enter the series, this patient first gave her age as 36; actually she was 46 years old. The rate for cervical cancer in the 45 year age group in Puerto Rico is now 1.18 per 1,000 women per year, though only 0.25 at the average age for our group. Two cases during 698 woman-years of experience is well within the limits of what may be expected from chance alone.

Unpleasant but benign side effects. Epigastric distress, nausea, and vomiting; headaches and dizziness; changes in accustomed menstrual pattern, including premenstrual tension and nervousness; pelvic pain; chloasma; and changes in weight and appetite were the more common side effects noted (Table II).

Some complaint was recorded in 18 per cent of the cycles; of the 550 users, 388 or 71 per cent voiced such complaints at least once. Symptoms were most common during the first 3 months of use, but could occur at any time, even after 30 months of trouble-free use. Withdrawals from the study because of side effects were at the rate of 6 per cent of cases in the first month of experience, 4 per cent in the second, 3 per cent in the third, and 1 per cent each month thereafter. Women of the R series and those

Table II. Increase and decrease of symptoms associated with use of norethynodrel*

	Per cent patients reporting	
	Increase	Decrease
<i>Reproductive system</i>		
Menstrual flow	6	43
Menstrual pain	11	17
Other menstrual symptoms	28	1
Breakthrough bleeding	20	0
Pelvic pain	12	3
Vaginal discharge	9	4
Contact bleeding	5	0
Libido	7	11
<i>Gastrointestinal system</i>		
Nausea	45	2
Vomiting	17	1
Gastralgia	24	1
Appetite	12	15
Weight	20	16
<i>Nervous system</i>		
Headache	28	2
Dizziness	29	1
<i>Skin</i>		
Chloasma	8	0

*Of 550 women, the number reporting varied from 350 commenting on chloasma to 441 reporting on nausea. Percentages are in terms of women actually reporting.

Table III. Reported reasons for discontinuing norethynodrel

<i>Reasons</i>	<i>Persons reporting each reason</i>	<i>Per cent of all users</i>
<i>Inherent in individual</i>	98	18
Moved away	45	8.2
Separated or widowed	17	3.1
To be sterilized*	14	2.5
Found to be pregnant	11	2.0
To get pregnant	7	1.3
Menopause	2	0.4
Died	2	0.4
<i>Inherent in community</i>	77	14
Frightened by rumors	35	6.4
Difficulty in securing supplies	20	3.6
Advice of physician	12	2.2
Religious aversion	10	1.8
<i>Inherent in method</i>	138	25
Unpleasant side effects	121	22.0
Vague and indefinite reasons	17	3.1
<i>Totals</i>		
Reasons given	313	
Persons discontinuing	267	49

*These persons, originally planning to be sterilized, were persuaded to use norethynodrel in order that the effect of medication could be determined through ovarian biopsies during their salpingectomy operations. Another 24 persons withdrew for other reasons and were subsequently sterilized.

in the P series receiving 5 mg. dosage from the outset have shown only two thirds the average withdrawal rate. Users described most symptoms as likely to be more severe when starting a medication cycle or in the interval between the twentieth tablet and the following menses, that is, during a change of the hormonal level of the body. For 121 persons, 22 per cent of all users, side effects were so unpleasant that the method was discarded. The other 267 complainers, finding the reactions could be tolerated until they disappeared, continued the method, at least until some other reason for stopping occurred (Table III).

Many of the changes observed are commonly associated with early pregnancy, for example, nausea, vomiting, dizziness, headache, increased vaginal discharge, and chloasma. Patients frequently volunteered that they felt pregnant. Softening and bluing of the cervix occasionally led other doctors examining these women to make a diagnosis of early pregnancy whereupon contraceptive treatment was stopped and the women did become pregnant.

Some symptoms of early pregnancy are influenced by emotional factors. To measure this effect on recipients of norethynodrel,¹⁹ Paniagua²⁰ in San Juan, Puerto Rico, gave 13 women 10 mg. norethynodrel tablets for 30 menstrual cycles and to another 15 women placebo tablets of identical appearance. All women continued their previous contraceptive practices. The women receiving placebos reported breakthrough bleeding (menstrual type discharge occurring in midcycle) in 5 per cent and other symptoms in 17 per cent of their cycles, as compared with breakthrough bleeding in 17 per cent and other symptoms in 23 per cent of the medicated cycles. Psychosomatic influence, inevitable in trials of a new drug, especially one under popular criticism, is suggested by these results. However, the occurrence of fully objective signs indicates that a definite group of physiological changes, sometimes unpleasant, is associated with the new hormone balance.

The menstrual periods following the

periodic interruption of the hormone are anovulatory bleeding rather than normal postovulatory periods; they usually occur on the fourth or fifth day after the 10 mg. tablets are stopped and on the first or second day after the 5 mg. tablets are stopped. In nearly 1 per cent of the observed cessations of medication no bleeding occurred within 10 days.

The most frequently reported effect on the menstrual pattern is decreased flow, reported by 43 per cent of users. Sometimes this affords relief from previous heavy blood loss, but other women need reassurance, because in Puerto Rico menstrual flow is usually interpreted as the body "ridding itself of bad humors" and hence thought desirable. Increased premenstrual tension and nervousness were the most common "other menstrual symptoms" of 28 per cent of reporting users. A few women reported increased tenderness and fullness of the breasts. Banks and associates¹ reported this symptom in 22 patients taking norethynodrel; others^{5, 17, 23-25, 35, 36} find it rarely.

Contact bleeding (bleeding after intercourse or pelvic examination) was an indication of severe cervical erosion. Slight erosions were found in 39 per cent of 456 women whose cervixes were examined before they were given norethynodrel and in 48 per cent of 114 women after an average of one year's experience. Moderate to severe erosions were found in an additional 10 per cent of women at the preliminary examinations and in 22 per cent of those after experience. All the women with contact bleeding (5 per cent of those reporting on this sign) were from this group with moderate to severe erosions. Of 183 women with erosions who were followed for more than one observation 45 per cent remained the same, all with minimal erosions; 40 per cent, who were not cauterized, became worse; and 15 per cent improved when norethynodrel was stopped, or after cauterization.

With use of norethynodrel, as in pregnancy, the cervix softens and erosions become larger and more succulent. From this experience we believe users of norethynodrel

Table IV. Persons discontinuing medication, and final physical examinations of women and of babies born after medication (by duration of use of norethynodrel)

Months of use of norethynodrel	Women using norethynodrel			Women given final physical examinations	Babies examined, con- ceived after medication for time shown
	At start of period	Discontinuing			
		No.	%		
1-3	550	118	21.4	37	38
4-6	410	43	10.5	19	13
7-9	304	21	6.9	17	2
10-12	260	26	10.0	45	2
13-15	184	18	9.8	11	1
16-18	156	9	5.8	25	1
19-21	119	12	10.1	16	1
22-24	91	7	7.7	8	
25-27	74	6	8.1	7	
28-30	56	4	7.1	2	
31-33	43	3	7.0	7	
34-36	16	0	0.0	4	
Total		267		198	58
Per cent of all users		49%		36%	

should have pelvic examinations at least once a year, with cauterization of erosions.

Nausea and vomiting were the side effects most frequently responsible for the patient's stopping norethynodrel. Antacids reduced the severity and incidence of nausea and gastralgia to tolerable levels.

One out of every 12 users developed or found increasing the patchy brown discoloration of the cheeks (chloasma), common during pregnancy among lighter Puerto Rican women. This was noted at various times from one to 33 months (average 16 months) after the method was started.

Two women, aged 40 and 45 years, underwent normal menopause while taking norethynodrel.

Synthetic progesterone-like steroids, used over long periods to treat complications of pregnancy, have been associated with male-like abnormalities of the genitals of female babies.^{9, 38} Of those reported only one was associated with norethynodrel. The findings are no contraindication to use of norethynodrel in fertility control since it is not prescribed for use during pregnancy. In 4 of the present cases medication continued after conception for periods up to 2 months. All 58 babies born to mothers in our series after use of norethynodrel have been examined by medical personnel, in most instances by

the authors. One infant had a clubfoot; no abnormalities of other parts, including the female genitals, were found (Table IV).

Comparison of reports of side effects. Investigators^{5, 23, 35, 36} of 17 α -ethinyl-19-nortestosterone report significantly fewer gastrointestinal disturbances than we found with norethynodrel. When 17 α -ethinyl-19-nortestosterone was used without estrogen, irregular bleeding was reported⁵ more frequently than by our users. Because different criteria for reportable side effects and different bases for expressing their frequency are used,^{1, 5, 19, 20, 22-25, 35, 36} no simple comparison of other effects can be made.

Reversibility. After stopping norethynodrel, 134 women continued at risk of pregnancy without contraception. They had used norethynodrel for an average of 7 and a maximum of 33 months. Of these, 106, or 79 per cent, became pregnant within an average interval of 4 months, and 58 were pregnant within 2 months or fewer than three menstruations after discontinuation of norethynodrel. (If no more than one menstruation followed discontinuance the interval was counted as one month.) The 28 women not becoming pregnant have been observed for an average of 7 and a median of 4 months after discontinuance. The 4 women who had used the method the longest (29,

30, 31, and 33 months) all became pregnant within one month of stopping. No inhibitory effect of norethynodrel on fertility was evident even after 2 years of use.

Of the 106 observed pregnancies 7 ended in abortion, one in a premature birth (to a woman whose 4 previous babies were premature), and one in a stillbirth due to arrest of the aftercoming head. Two cases of placental retention and one of threatened premature delivery at 8 months also occurred, with no adverse effects. Before using norethynodrel, women in our study had a frequency of 10 abortions and 2 stillbirths per 100 pregnancies. It follows that use of norethynodrel before or even during early pregnancy led to no increase in complications of pregnancy or delivery.

Initial acceptability. Out of 195 households in the first two areas surveyed for the R series 133 women were eligible for the trial and 110 or 83 per cent began the method. These areas were subsequently cleared by the municipality, and most inhabitants have been forced to move. Yet in March, 1960, 18 months to 3 years after starting, 66 or 60 per cent of these 110 women were still using norethynodrel. Three other areas subsequently surveyed had a lower initial rate of acceptance, 39 to 57 per cent. During these latter surveys, in March, 1959, television programs and newspaper articles occurred opposing contraception, especially by this oral method. The result was a temporary increased discontinuance and a marked, though brief, decrease in accessions, especially in the P series.

Acceptability after trial. Out of the balance of influences which determine whether or not a given woman will continue the method, certain discouraging factors are clear. The chief reasons given for stopping were the unpleasant side effects, difficulty in returning for supplies, and lack of confidence in the safety of norethynodrel. That women will tire of taking tablets every day for long periods might be expected from experience with mass malaria prophylaxis; few of these women, however, have reported such feelings (Table IV).

The proportion of persons discontinuing norethynodrel for reasons inherent in community and method was significantly less in the R series than in the P group. Frequent visits by one social worker to the R series homes with reassurance about unpleasant symptoms, and convenience in securing supplies were important factors in this difference.

A measure of the acceptability of any method is the rate at which it is abandoned. This was 10 per cent in the first month, 6 per cent in each of the next 2 months, and approximately 3 per cent each month thereafter. Of all persons discontinuing, side effects were responsible for two thirds of discontinuances during the first 3 months and one third in the months thereafter.

Pregnancies prevented. The ratio of observed to expected pregnancies is a measure of the effectiveness of the program. In their preceding married lives during which their average age was 24 years, the users of norethynodrel had had 59 pregnancies per 100 woman-years. The first significant drop in fertility in Puerto Rico occurs after age 30 years, a greater age than the average for women of this series at the end of the study. The preceding rate thus may be used as a base for comparison. During 518 woman-years of experience 316 pregnancies would be expected, and 90 per cent or 284 would have resulted in live births. Only 11 children were born. Use of norethynodrel by the 550 women has apparently prevented the birth of 273 unwanted children.

Summary

A combination of 9.85 mg. of norethynodrel with 0.15 mg. of ethynylestradiol-3-methyl ether or of 5.0 mg. of norethynodrel with 0.075 mg. of ethynylestradiol-3-methyl ether was taken by mouth for 20 days each month by 550 women of proved fertility. Eleven pregnancies occurred in a total of 518 woman-years of use; 4 women were pregnant before starting the program and 7 failed to follow instructions.

Nausea, gastralgia, headache, dizziness, or other symptoms were reported one or more

times by 71 per cent of all users. These were sufficiently severe to lead 22 per cent of users to discontinue the tablet; for the remainder the side effects proved tolerable and subsided within a few months. No lasting ill effect could be attributed to the medication.

Pregnancy usually occurred promptly after discontinuation of norethynodrel; 79 per cent of the women at risk were pregnant after a mean of 4 months. Abnormal pregnancies and deliveries were within usual

limits; the children born had no abnormalities that could be ascribed to norethynodrel.

Norethynodrel has proved in this field trial an effective, safe, reversible, and fairly acceptable method for the spacing of births. Its suitability in public health programs, applicable to a community within the usual resources of funds, physicians, and the habits of people remains to be tested.

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Spermicidal effectiveness of chemical contraceptives used with the firm cervical cap

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WHILE the clinical effectiveness of the rigid cervical cap method as a contraceptive seems to have been well established by several studies,^{2, 4, 6} the exact mechanism by which protection is obtained has not been clearly explained. Is twofold protection afforded by the mechanical device (cervical cap) plus the spermicidal cream or jelly used in conjunction with it, or is it chiefly the mechanical obstacle that affords the protection?

Most clinicians using the cap advise putting a chemical contraceptive inside it, but very few investigations have been made of how long the contraceptive retains its spermicidal power while the cap is in position.

Since in many instances the cervical cap remains in place from the end of one menstrual period to the beginning of the next, as long as 20 days or more, it must be assumed that a considerable part, if not all, of the contraceptive chemical is absorbed or lost, thereby diminishing, if not eliminating, its spermicidal effect.

Previous observers have given thought to this problem. Novak,⁵ in 1924, investigated cervical cap contents in 30 cases; 23 of these showed acid reaction, 3 were slightly alkaline, and 4 had neutral reaction. The acidity

of the contents of the cervical cap was thought to be an important factor in contraceptive effectiveness. Novak observed that the motility of the spermatozoa was stopped within a few minutes by the acid contents of the cap. Bauer¹ reported in 1930 on a spermicidal paste specifically prepared for use with the cervical cap; he was able to demonstrate traces of this substance in the contents of the cap as late as 14 days after insertion.

To our knowledge, no work has been published in which modern methods of testing spermicidal activity were used to investigate the contents of cervical caps. In India, a cervical cap test was recently devised by the contraceptive testing center of the government; this test, however, is concerned only with the harmlessness, not the effectiveness, of the method.³

We have applied a modified spermicidal testing method to the investigation of the contents of 69 cervical caps worn by 50 women and recovered from 7 to 28 days after insertion.* Six different commercial chemical contraceptives were used—3 jellies and 3 creams. Three sizes of rigid cervical caps—24, 30, and 36 mm. in diameter—

*A similar procedure can be employed in order to determine for how many hours spermicidal jellies or creams inserted with a diaphragm keep their potency. This knowledge is important for women who keep the diaphragm in position during several cohabitations. For this test, the patient is instructed to insert diaphragm-and-chemical a few hours before her return visit to the clinic, where the spermatoxic chemical is simply scraped off the diaphragm for investigation.

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made of Lucite, a clear plastic material, in the shape of a truncated cone with a narrow smooth-edged rim, were used to fit the cervix. The cap was filled to a quarter or a third of its capacity with 2.5 to 5 ml. of the contraceptive jelly or cream at the time of insertion by the physician.

Testing procedure

Our early findings indicated that, regardless of the contraceptive preparation used inside the cap, almost no spermicidal effect was present after a longer period than 7 days. Of 13 caps whose contents were examined from 14 to 28 days after insertion, only one, with cream, showed contents possessing spermicidal activity, 14 days after insertion. The other 55 caps, therefore, were all investigated on the seventh day after insertion.

After speculum observation to make sure the cervical cap still covered the cervix, the cap was removed and its contents placed in a clean stoppered glass vial and refrigerated (below 4° C.) until used by the laboratory—usually within a week, the time depending on the availability of suitable semen.

The quality standard used for semen was as follows: Sample age: not over 3 hours after ejaculation; motility: grade 3, 60 per cent or more; count: 60 million or more spermatozoa per milliliter; resistance: motility continued for more than 15 minutes at room temperature after mixing with an equal volume of 2.8 per cent potassium acid phthalate solution.

In the laboratory, at room temperature, the material from the cervical cap was diluted with an equal volume of saline (0.9 per cent NaCl). With a pipette, 0.3 ml. of semen was placed in the bottom of a Kahn tube (12 mm. inside diameter, 8.5 mm. long) together with a loosely fitting cadmium-plated shockproof steel lock washer. The nine projections extending inward from the rim of the washer made possible its rotation by an alternating current electromagnetic mixer. At "zero time," an equal volume (0.3 ml.) of the diluted material from the

cervical cap was added, and simultaneously the mixer was connected to rotate the washer. At the end of 10 seconds, a small drop of the resulting mixture—cap contents, saline, and semen in the proportions of 1:1:2—was transferred by means of a glass rod to a slide, covered with a coverslip, and observed under dry high power ($\times 600$).

For the purpose of this study, the criterion for a positive test (material having spermicidal power) was arbitrarily fixed as the immobilization of spermatozoa in this 1:1:2 dilution within 2 minutes after "zero time." This criterion represents a standard much lower than the values recorded in our laboratory during previous tests of the spermicidal powers of these same jellies and creams. Complete immobilization occurred *within 20 seconds*, after similar 10 second electromagnetic mixing at room temperature, in the following proportions of contraceptive materials, saline, and semen: Delfen Cream 1:99:20; Kemi-Cream 1:4:1; Koromex Jelly 1:29:6; Laktikol Jelly 1:34:7; Ortho-Creme 1:29:6; Ortho-Gynol Jelly 1:34:7.

Table I. Spermicidal power of contraceptive jelly residues from cervical caps

Jelly	No. of days worn	No. of caps	Negative	Positive
Koromex	7	7	7	0
Laktikol	7	5	5	0
	14	1	1	0
Ortho-Gynol	7	7	7	0
Total		20	20	0

Table II. Spermicidal power of contraceptive cream residues from cervical caps

Cream	No. of days worn	No. of caps	Negative	Positive
Delfen	7	8	4	4
Kemi-Cream	21	1	1	0
	22	1	1	0
	28	2	2	0
Ortho-Creme	7	29	25	4
	14	5	4	1
	21	3	3	0
Total		49	40	9

Findings

As shown in Table I, 20 tests were carried on cervical caps with jelly—19 worn for 7 days each, one for 14 days. In none of the contents of these 20 caps was any spermicidal power found.

Table II shows the findings obtained from the contents of the 49 caps used with creams—36 worn for 7 days each, 5 for 14 days, and 7 for 21 to 28 days. Among these 49, 9 showed positive spermicidal power. In only one of the 12 cases tested at 14 days or later was spermicidal power found.

Comment

Our study showed that when contraceptive jellies were used inside the cervical cap no spermicidal activity was detectable with the technique used after 7 days. With contraceptive creams, spermicidal activity could still be noted after 7 days in 9 of 49 tests. It seemed possible that the difference found between jellies and creams is due to the physical rather than to the chemical characteristics of the vehicles. In the residues of caps that had been worn 7 days and longer, remnants of unresorbed cream—but never of jelly—were detected macroscopically and microscopically.

Since the cap is usually inserted soon after

menstruation, and so few of our tests showed spermicidal capacity after 7 days of use, it can be assumed that for most women the contraceptive chemicals are likely to be exhausted at the time of ovulation, and that the satisfactory contraceptive protection afforded by the cervical cap, as shown by previous studies,^{2, 4, 6} does not need a spermicidal supplement.

Summary

1. No spermicidal power was found in the contents of 20 firm plastic cervical caps after they had been worn for 7 days with one of three different commercial contraceptive jellies.

2. In less than one fifth of the tests in which commercial contraceptive creams were used, spermicidal power was found after 7 days—in one case, after 14 days.

3. The low proportion of tests showing spermicidal power after 7 days and the contraceptive protection found in clinical tests^{2, 4, 6} suggest that the cap affords protection without a spermicidal supplement.

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